INDENE DERIVATIVES AS PHARMACEUTICAL AGENTS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Patent Application No. 60/463,216, filed April 15, 2003, where this provisional application is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is directed to indene derivatives, methods of using the derivatives and pharmaceutical compositions containing same.

Description of the Related Art

The normal inflammatory response is an essential localized host response to invading microorganisms or tissue injury which involves cells of the immune system. The inflammatory response allows the body to specifically recognize and eliminate an invading organism and/or repair tissue injury. The classic signs of inflammation include redness (erythema), swelling (edema), pain and increased heat production (pyrema) at the site of injury. Many of the acute changes at the site of inflammation are either directly or indirectly attributable to the massive influx of leukocytes (*e.g.*, neutrophils, eosinophils, lymphocytes, monocytes) which is intrinsic to this response. Leukocytic infiltration and accumulation in tissue results in their activation and subsequent release of inflammatory mediators such as LTB_4, prostaglandins, TNF-α, IL-1β, IL-8, IL-5, IL-6, histamine, proteases and reactive oxygen species for example.

Normal inflammation is a highly regulated process that is tightly controlled at several levels for each of the cell types involved in the response. For example, expression of the pro-inflammatory cytokine TNF-α is controlled at the level of gene expression, translation, post-translational modification, and release of the mature form from the cell membrane. Pro-inflammatory responses are normally countered by

endogenous anti-inflammatory mechanisms such as generation of IL-10 or IL-4. A characteristic of a normal inflammatory response is that it is temporary in nature and is followed by a resolution phase which brings the state of the tissue back to its prior condition. The resolution phase is thought to involve up-regulation of anti-inflammatory mechanisms, such as IL-10, as well as down-regulation of the pro-inflammatory processes.

Inflammatory disease occurs when an inflammatory response is initiated that is inappropriate and/or does not resolve in the normal manner, but rather persists and results in a chronic inflammatory state. Disease may also involve a perturbation of the cellular immune response that results in recognition of host proteins (antigens) as foreign. Here, the inflammatory response becomes misdirected at host tissues with effector cells targeting specific organs or tissues often resulting in irreversible damage. The self-recognition aspect of auto-immune disease is often reflected by the clonal expansion of T-cell subsets characterized by a particular T-cell receptor (TCR) subtype in the disease state. Often inflammatory disease is also characterized by an imbalance in the levels of T-helper (Th) subsets (*i.e.*, Th1 cells vs. Th2 cells). Inflammatory disease may be systemic (*e.g.* lupus) or localized to particular tissues or organs (*e.g.* asthma), and exerts an enormous personal and economic burden on society. Examples of some of the most common and problematic inflammatory diseases are asthma, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, psoriasis, and atopic dermatitis.

Therapeutic strategies aimed at curing inflammatory diseases usually fall into one of two categories: (a) down-modulation of processes that are up-regulated in the disease state or (b) up-regulation of anti-inflammatory pathways in the affected cells or tissues. Most regimes currently employed in the clinic fall into the first category. Some examples of which are corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs).

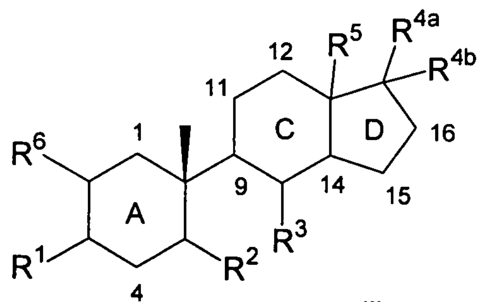
Many of the tissue, cellular and biochemical processes which are perturbed in inflammatory disease have been elucidated and this has allowed the development of experimental models or assays to mimic the disease state. These

assays and models enable screening and selection of compounds with a reasonable probability of therapeutic efficacy in the relevant inflammatory disease. Despite the use of these models, effective drugs have not been discovered for many inflammatory diseases. There is a significant need for therapeutic agents that effectively arrest or reverse disease progression for disease states or pathologies such as asthma, chronic obstructive pulmonary disease, multiple sclerosis, psoriasis, and inflammatory bowel disease.

BRIEF SUMMARY OF THE INVENTION

The compounds of the present invention are useful as anti-inflammatory agents.

Accordingly, in one aspect the invention provides compounds of formula (I):



(I)

wherein:

the A, C or D ring is independently fully saturated, partially saturated or fully unsaturated;

C1, C4, C11, C12, C15 and C16 are each independently substituted with two of the following, which are independently selected: hydrogen, alkyl, $-R^8-OR^7$, or $-R^8-N(R^7)_2$, provided that C4 is not substituted by two methyl groups;

C9 and C14 are each independently substituted with hydrogen, alkyl, $-R^8-OR^7$, or $-R^8-N(R^7)_2$;

R^1 is $-OR^7$ or $-N(R^7)_2$;

R^2 and R^3 are each independently selected from the group consisting of

$-R^8-OR^7$, $-R^8-OC(O)R^9$, $-R^{10}-N(R^7)_2$, $-R^{10}-N(R^9)C(O)R^9$, $-R^{10}-N(R^9)S(O)_tR^9$ (where t is 1 or 2), $-R^{10}-N(R^9)C(NR^9)N(R^9)_2$, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, and optionally substituted heteroarylalkenyl;

R^{4a} and R^{4b} are each independently selected from hydrogen, alkyl, alkenyl or alkynyl;

or R^{4a} is hydrogen, alkyl, alkenyl or alkynyl and R^{4b} is a direct bond to the carbon at C16;

or R^{4a} and R^{4b} together form alkylidene or haloalkylidene;

R^5 is alkyl or R^5 is a direct bond to the carbon at C14;

R^6 is hydrogen, $-R^8-OR^7$ or $-R^8-N(R^7)_2$;

each R^7 is independently selected from the group consisting of hydrogen, $-R^{10}-OR^9$, $-R^{10}-N(R^9)_2$, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

each R^8 is independently selected from the group consisting of a direct bond, a straight or branched alkylene chain, and a straight or branched alkenylene chain; and

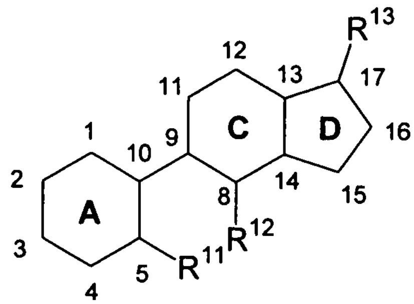
each R^9 is independently selected from the group consisting of hydrogen, alkyl, aryl and aralkyl;

each R^{10} is independently selected from the group consisting of a straight or branched alkylene and a straight or branched alkenylene chain;

as a single stereoisomer, a mixture of stereoisomers, or as a racemic mixture of stereoisomers;

or a pharmaceutically acceptable salt, solvate or prodrug thereof, in isolation or in a mixture.

In another aspect, the invention provides compounds of formula (II):



(II)

wherein:

the A, C or D ring is independently fully saturated, partially saturated or fully unsaturated;

C1, C2, C4, C11, C12, C15 and C16 are each independently substituted with:

(a) one of the following: =O, $=C(R^{14})_2$, $=C=C(R^{14})_2$, $-[C(R^{14})_2]_n-$ (where n is 2 to 6) and $-O-[C(R^{14})_2]_m-O-$ (where m is 1 to 6); or

(b) two of the following, which are independently selected: $-R^{14}$, $-OR^{15}$ and $-N(R^{16})_2$;

C3 is substituted with two of the following, independently selected: $-R^{14}$, $-OR^{15}$ and $-N(R^{16})_2$;

C5, C8, C9, C10, C13, C14 and C17 are each independently optionally substituted with one of the following: $-R^{14}$, $-OR^{15}$ and $-N(R^{16})_2$;

R^{11} and R^{12} are each independently selected from the group consisting of hydrogen, halo, =O, $-OR^{15}$, $-N(R^{16})_2$ and a C_{1-30} organic moiety;

R^{13} is $-R^{14}$, $-OR^{15}$, $-N(R^{16})_2$, $=C(R^{14})_2$, $=C=C(R^{14})_2$, $-[C(R^{14})_2]_n-$ (where n is 2 to 5) or $-O-[C(R^{14})_2]_m-O-$ (where m is 1 to 5);

each R^{14} is independently selected from hydrogen, halo and C_{1-30} organic moiety where two geminal R^{14} groups may together form a ring with the carbon to which they are attached;

each R^{15} is independently selected from the group consisting of hydrogen, an oxygen protecting group such that $-OR^{15}$ is a protected hydroxy group, a leaving group initiator such that $-OR^{15}$ is a leaving group and a C_{1-30} organic moiety that may

optionally contain at least one heteroatom selected from the group consisting of boron, halogen, nitrogen, oxygen, phosphorus, silicon and sulfur, where vicinal $-OR^{15}$ groups together with the carbons to which they are attached may form a cyclic structure that protects vicinal hydroxy groups and where geminal $-OR^{15}$ groups together with the carbon to which they are attached, may form a cyclic structure that protects a carbonyl group;

each R^{16} is independently selected from the group consisting of hydrogen, $-OR^{17}$, oxygen (so as to form a nitro or an oxime group), and a C_{1-30} organic moiety that may optionally contain at least one heteroatom selected from the group consisting of boron, halogen, nitrogen, oxygen, phosphorus, silicon and sulfur; or

two R^{16} groups, together with the nitrogen to which they are attached, form a heterocyclic ring; and

each R^{17} is independently selected from hydrogen and a C_{1-30} hydrocarbyl; as a single stereoisomer, a mixture of stereoisomers, or as a racemic mixture of stereoisomers;

or a pharmaceutically acceptable salt, solvate or prodrug thereof, in isolation or in a mixture;

provided, however, that

(1). C4 can not be substituted with two methyl groups

(2) R^{13} can not be =O or 6-methylhept-2-yl;

(3) when C17 is substituted with hydrogen, R^{13} can not be -OH or -OC(O)R where R is methyl, ethyl, phenyl or cyclohexyl;

(4) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and hydroxy, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is =O, and R^{12} is $-CH_2C(O)H$, R^{13} can not be $-C(CH_3)HCH_2CH_2C(O)OCH_3$ or $-C(CH_3)HCH_2CH_2C(CH_2CH_3)HC(CH_3)_2H$;

(5) when C1, C2, C4, C11, C12, and C15 are each substituted with two hydrogens, C16 is substituted with hydrogen and hydroxy, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, C3 is

substituted with hydrogen and hydroxy, R^{11} is =O, and R^{12} is $-CH_2C(O)OH$ or $-CH_2C(O)OCH_3$, R^{13} can not be $-C(CH_3)HNHCH_2CH_2N(CH_3)_2$, $-C(CH_3)HCH_2CH_2C(CH_2CH_3)HC(CH_3)_2H$, or $-C(CH_3)H-R$ (where R is 5-methylpiperidin-2-yl);

(6) when C1, C2, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and hydroxy, C4 is substituted with two hydrogens or C4 is double bonded to C3, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is =O, and R^{12} is $-CH_2CN$, R^{13} can not be $-C(O)OCH_3$;

(7) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and hydroxy, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is =O, and R^{12} is =CHC(O)H, R^{13} can not be $-C(CH_3)HCHCHC(CH_3)HC(CH_3)_2H$;

(8) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and hydroxy, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is =O, and R^{12} is $-CH_2CH_3$, R^{13} can not be $-C(CH_3)HOC(O)CH_3$;

(9) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and hydroxy, C5, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is hydroxy, and R^{12} is $=CHCH_2OH$, R^{13} can not be $-C(CH_3)HCH_2CH_2C(CH_2CH_3)HC(CH_3)_2H$, or $-C(CH_3)HCHCHC(CH_3)HC(CH_3)_2H$, $-C(CH_3)HCH_2CH_2C(CH_2)C(CH_3)_2H$, or $-C(CH_3)HCHC[CH_2C(CH_3)_2H]H$;

(10) when C1, C2, C4, C11, C12, and C15 are each substituted with two hydrogens, C3 is substituted with hydrogen and hydroxy, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, C16 is substituted with two hydrogens or with one hydrogen and hydroxy, R^{11} is hydroxy, and R^{12} is $-CH_2CH_2OH$, R^{13} can not be $-C(CH_3)HCH_2CH_2C(CH_2CH_3)HC(CH_3)_2H$, $-C(CH_3)HCH_2OH$, $-CH_2OH$, or $-C(CH_3)H-R$ (where R is 5-methylpiperidin-2-yl);

(11) when C1, C2, C4, C11, C12, C15 and C16 are each substituted

with two hydrogens, C3 is substituted with hydrogen and hydroxy, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is hydroxy, and R^{12} is $-CH_2CH_3$, R^{13} can not be $-C(CH_3)HCH_2C(CH_3)HC(CH_3)_2H$ or $-C(OH)HCH_3$;

(12) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and hydroxy, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is hydroxy, and R^{12} is $-CHCH_2$, R^{13} can not be $-C(OH)HCH_3$;

(13) when C1, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C2 is substituted with hydrogen and hydroxy, C3 is substituted with hydrogen and hydroxy, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is $-C(O)OH$, and R^{13} is $-C(CH_3)HC(OH)HC(OH)HC(CH_2CH_3)HC(CH_3)_2H$, R^{12} can not be $-CH_2SH$ or $-CH_2SSCH_2R$ (where R is hydrogen or a C_{1-30} organic moiety);

(14) when C1, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C2 is substituted with two hydrogens or with hydrogen and hydroxy, C3 is substituted with hydrogen and hydroxy, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is $-C(O)OH$ or $-CH_2OH$, and R^{12} is $-CH_2OH$, R^{13} can not be $-CH_2OH$, $-C(CH_3)HC(OH)HC(OH)HC(CH_3)HC(CH_3)_2H$ or $-C(CH_3)HC(OH)HC(OH)HC(CH_2CH_3)HC(CH_3)_2H$;

(15) when C1, C2, C11, C12 and C15 are each substituted with two hydrogens, C3 is substituted with hydrogen and hydroxy, C4 is substituted with hydrogen and methyl or with two hydrogens, C5 and C9 are each substituted with hydrogen, C8 and C14 are each substituted with hydrogen or each are substituted with methyl, C10 and C13 are each substituted with methyl, C16 is substituted with hydrogen and $-OC(O)CH_3$, R^{11} is $-C(O)H$, and R^{12} is $-C(O)H$, R^{13} can not be $=C[C(O)OH]CH_2CH_2CHC(CH_3)_2$ or $-C(CH_3)HCH_2CH_2C(O)OCH_3$;

(16) when C1, C2, C4, C11, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and hydroxy, C5, C8, C9, C14 and C17 are

each substituted with hydrogen, C10 and C13 are each substituted with methyl, C12 is substituted with hydrogen and hydroxy, R^{11} is $-CH_2C(O)OH$ or $-CH_2C(O)OCH_3$, and R^{12} is $-NH_2$ or $-N(CH_3)_3$, R^{13} can not be $-C(CH_3)HCH_2CH_2C(O)OCH_3$ or $-C(CH_3)HCH_2CH_2C(O)OH$;

(17) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and hydroxy, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is $-NH_2$ or $-N(CH_3)_2$, and R^{12} is $-CH_2C(O)OH$ or $-CH_2C(O)OCH_3$, R^{13} can not be $-C(CH_3)HCH_2CH_2C(O)OCH_3$ or $-C(CH_3)HCH_2CH_2C(O)OH$;

(18) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and hydroxy, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is $=NNHC(NH)NH_2$, and R^{12} is $-CH_2CH_2C(O)OH$, R^{13} can not be $-C(CH_3)NNHC(NH)NH_2)$;

(19a) when C1, C2, C4, C11 and C12 are each substituted with two hydrogens, C3 is substituted with =O, C8, C14 and C17 are each substituted with hydrogen, C9 is substituted with hydrogen or hydroxy, C10 and C13 are each substituted with methyl, C15 is substituted with two hydrogens or C15 is substituted with hydrogen and double bonded to C16, C16 is substituted with hydrogen or hydroxy and is double bonded to C15 or C16 is substituted with $=CH_2OH$, R^{11} is =O, and R^{12} is $=CHC(O)OH$, R^{13} can not be $-C(CH_3)HC(O)CH_2C(CH_3)HC(CH_3)_2H$;

(19b) when C1, C2, C4, C11 and C12 are each substituted with two hydrogens, C3 is substituted with =O, C8 and C14 are double bonded to each other, C9 is substituted with hydroxy, C10 and C13 are each substituted with methyl, C15 is substituted with hydrogen and double bonded to C16, C16 is substituted with methoxy and double bonded to C15, C17 is substituted with hydrogen, R^{11} is =O, and R^{12} is $-CH_2C(O)OCH_3$, R^{13} can not be $-C(CH_3)HC(O)CH_2C(CH_3)HC(CH_3)_2H$;

(20) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with =O, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is =O,

and R^{12} is $-CH_2CN$, R^{13} can not be -C(O)NHR (where R is 5-trifluoromethyl-2-*t*-butylphenyl) or $-C(O)OCH_3$;

(21) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with =O, C8, C9, C14 and C17 are each substituted with hydrogen, C10 is substituted with methyl or $-CH_2OC(O)H$, C13 is substituted with methyl, R^{11} is =O, and R^{12} is $-CH_2CH_3$ or $-CH_2I$, R^{13} can not be $-C(O)CH_3$;

(22) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with =O, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is -C(O)OH, and R^{12} is -C(O)OH, R^{13} can not be $-C(CH_3)HCH_2CH_2C(O)OH$ or $-C(CH_3)HCH_2CH_2CH_3$;

(23) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with =O, C5, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is -CN, and R^{12} is =O, R^{13} can not be $-C(CH_3)HCHCHC(CH_3)HC(CH_3)_2H$;

(24) when C1, C2, C4, C12 and C15 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OC(O)CH_3$, C8, C9, and C14 are each substituted with hydrogen, C11 is substituted with two hydrogens, hydrogen and hydroxy, or hydrogen and $-OC(O)CH_3$, C16 is substituted with two hydrogens or $=CH_2$, C17 is substituted with hydrogen, hydroxy or $-OC(O)CH_3$, C10 and C13 are each substituted with methyl, R^{11} is =O, and R^{12} is $-CH_2C(O)OH$, R^{13} can not be $-CH_3$, $-CH_2CH_3$, $-C(O)CH_3$, cyclopentanone, $-C(CH_3)HOC(O)R$ (where R is phenyl), $-C(CH_3)HCH_2CH_2C(O)OCH_3$, $-C(O)CH_2OC(O)CH_3$ or $-C(CH_3)HCH_2CH_2C(CH_2CH_3)HC(CH_3)_2H$;

(25) when C1, C2, C4, C11, C12 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OC(O)CH_3$, C8 and C9 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, C14 is substituted with methyl or $-OC(O)CH_3$, C15 is substituted with two hydrogens or =O, C17 is substituted with hydrogen or $-OC(O)CH_3$, R^{11} is =O, and R^{12} is $-CH_2C(O)H$, R^{13}

can not be $-C(O)OCH_3$, $-C(O)CH_3$ or $-CH_3$;

(26) when C1, C2, C4, C11, C12, and C15 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OC(O)CH_3$, C8, C9, and C14 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, C16 is substituted with two hydrogens or forms a double bond with C17, R^{11} is =O, and R^{12} is $-CH_2CN$, R^{13} can not be $-C(O)CH_3$;

(27) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OC(O)CH_3$, C8, C9, C14 and C17 are each substituted with hydrogen, C10 is substituted with hydrogen or $-CH_2C(O)OH$, C13 is substituted with methyl, R^{11} is =O, and R^{12} is $-CH_2I$ or $-CH_2C(O)OCH_3$, R^{13} can not be $-C(O)CH_3$;

(28) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OC(O)CH_3$, C8, C9, C14 and C17 are each substituted with hydrogen, C10 is substituted with hydrogen or $-CH_2C(O)OH$, C13 is substituted with methyl, R^{11} is =O, and R^{12} is $-CH_2I$, $-CHCH_2$, $-CCH$, $-C(O)OCH_3$ or $-CH_2OCH_3$, R^{13} can not be $-C(CH_3)HOC(O)CH_3$

(29) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OC(O)CH_3$, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is =O, and R^{12} is $-CH_2NCO$, $-CH_2C(O)N_3$ or $-C(O)OH$, R^{13} can not be $-C(CH_3)HCH_2CH_2C(CH_2CH_3)HC(CH_3)_2H$;

(30) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OC(O)CH_3$, C8, C9, and C14 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, C17 is substituted with $-OC(O)CH_3$, R^{11} is =O, and R^{12} is $-CH_2CHNNHR$ (where R is 2,4-dinitrophenyl), R^{13} can not be $-CH_3$;

(31) when C1, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C2 is substituted with hydrogen and $-OC(O)CH_3$, C3 is substituted with hydrogen and $-OC(O)CH_3$, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is $-C(O)OH$, and R^{12} is

-C(O)H, R^{13} can not be $-C(CH_3)HCH_2CH_2CH_2CH_3$;

(32) when C1, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C2 is substituted with hydrogen and $-OC(O)CH_3$, C3 is substituted with hydrogen and $-OC(O)CH_3$, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is -C(O)OH or $-C(O)OCH_3$, and R^{12} is -C(O)H, $-CH_2SSCH_2R$ (where R is hydrogen or a C_{1-30} organic moiety), $-CH_2OS(O)_2CH_3$, or $-CH_2OH$, R^{13} can not be $-C(CH_3)HC[OC(O)CH_3]HC[OC(O)CH_3]HC(CH_2CH_3)HC(CH_3)_2H$;

(33) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OC(O)CH_3$, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is -C(O)OH, and R^{12} is -C(O)OH, R^{13} can not be $-C(CH_3)HCH_2CH_2C(O)OH$;

(34) when C1, C2, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OC(O)CH_3$, C4 is substituted with hydrogen and methyl, C5, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is $-CH_2C(O)H$, and R^{12} is =O, R^{13} can not be $-C(CH_3)HCH_2CH_2C(O)C(CH_3)_2H$;

(35) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OC(O)CH_3$, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, and R^{11} and R^{12} are both $-CHNOCH_3$ or $-CHNOCH_2CH_3$, R^{13} can not be $-C(CH_3)HCH_2CH_2C(O)OCH_3$;

(36) when C1, C2, C4, C11, C12 and C15 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OC(O)CH_3$, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, C16 is substituted with hydrogen and $-OC(O)CH_3$, R^{11} is $-OC(O)CH_3$, and R^{12} is $-CH_2CH_2OC(O)CH_3$, R^{13} can not be $-C(CH_3)HR$ (where R is 5-methyl-1-acetylpiperidin-2-yl);

(37) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and triisopropylsilyloxy, C8, C9,

C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is =O, and R^{12} is $-CH_2C(O)OH$, $-CH_2C(O)H$, $-CH_2CH_2N_3$, $-CH_2CH_2OH$, $-CH_2CH_2OS(O)_2CH_3$ or $-CH_2C(O)N_3$, R^{13} can not be $-C(O)N(CH_2CH_3)_2$;

(38) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and triisopropylsilyloxy, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is =O, and R^{12} is $-CH_2C(O)OH$, $-CH_2C(O)H$ or $-CH_2C(O)Cl$, R^{13} can not be $-C(O)OCH_3$;

(39) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and triisopropylsilyloxy, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, and R^{11} and R^{12} are both $-CHNOCH_3$, R^{13} can not be $-C(CH_3)HCH_2CH_2C(O)OCH_3$;

(40) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted hydrogen and -OC(O)R (where R is 4-nitrophenyl or 3,5-dinitrophenyl), C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is -OH, and R^{12} is $-CH_2CH_2OC(O)R$ (where R is 4-nitrophenyl or 3,5-dinitrophenyl), R^{13} can not be $-C(CH_3)HCH_2OC(O)R$ (where R is 4-nitrophenyl or 3,5-dinitrophenyl) or $-C(CH_3)HCH_2CH_2C(CH_2CH_3)HC(CH_3)_2H$;

(41) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OCH_2OCH_3$, C5, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is -CN, and R^{12} is -OH or =O, R^{13} can not be $-C(CH_3)HCHCHC(CH_3)HC(CH_3)_2H$;

(42) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OCH_2CH_2CH_3$, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is =O, and R^{12} is $-CH_2C(O)OH$, R^{13} can not be $-OCH_2CH_2CH_3$;

(43) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with =NNHR (where is R is 2,4-dinitrophenyl), C5,

C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, and R^{11} and R^{12} are both -C(O)OH, R^{13} can not be $-C(CH_3)HCH_2CH_2C(O)OH$;

(44) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OCH_2R$ (where R is phenyl), C5, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is $-CH_2C(O)H$, and R^{12} is =O, R^{13} can not be $-C(CH_3)HCH_2CH_2C(CH_3)HC(CH_3)_2H$;

(45) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-CH_3$, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is =O, and R^{12} is -C(O)OH, R^{13} can not be $-OC(CH_3)_3$; and

(46) when C1, C2, C4, C11, C12, C15 and C16 are each substituted with two hydrogens, C3 is substituted with hydrogen and $-OC(CH_3)_3$, C5, C8, C9, C14 and C17 are each substituted with hydrogen, C10 and C13 are each substituted with methyl, R^{11} is hydroxy, and R^{12} is $-CH_2OH$, R^{13} can not be $-OC(CH_3)_3$.

In another aspect, the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable excipient and a compound of formula (I) or a compound of formula (II), as described above.

In another aspect, the invention provides a method of treating an inflammatory condition or disease in a mammal, which method comprises administering to the mammal in need thereof a therapeutically effective amount of a compound of formula (I) or a compound of formula (II), as described above.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides pharmaceutical compositions and methods useful in the treatment and/or prevention of various disease conditions. For example, in one aspect, the present invention provides a method of treating inflammation in a mammal, preferably a human. The method includes administering to a mammal in need thereof a therapeutically effective amount of a compound of the invention or a

pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition containing a compound of the invention or a pharmaceutically acceptable salt thereof.

Before describing the invention in further detail, certain definitions as used herein are provided with the following definitions, and certain conventions used herein are also set forth.

Definition of terms

As used herein the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. For example, "a compound" refers to one or more of such compounds, while "the enzyme" includes a particular enzyme as well as other family members and equivalents thereof as known to those skilled in the art. As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated.

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to seven carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), and the like.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, having from two to seven carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

"Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to seven carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, ethynyl, prop-2-ynyl, but-2-ynyl, pent-2-ynyl, penta-1,4-diynyl, and the like.

"Aryl" refers to refers to aromatic monocyclic or multicyclic hydrocarbon

ring system consisting only of hydrogen and carbon and containing from 6 to 19 carbon atoms, where the ring system may be partially or fully saturated. Aryl groups include, but are not limited to groups such as fluorenyl, phenyl and naphthyl.. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, $-R^8-OR^7$, $-R^8-N(R^7)_2$, $-R^8-C(O)R^7$, $-R^8-C(O)OR^7$, $-R^8-C(O)N(R^7)_2$, $-R^8-N(R^9)C(O)OR^9$, $-R^8-N(R^9)C(O)R^9$, $-R^8-N(R^9)(S(O)_tR^9)$ (where t is 1 to 2), $-R^8-S(O)_pOR^9$ (where p is 1 to 2), $-R^8-S(O)_tR^9$ (where t is 0 to 2), and $-R^8-S(O)_pN(R^9)_2$ (where p is 1 to 2) where each R^7, R^8 and R^9 is as defined above in the Summary of the Invention.

"Aralkyl" refers to a radical of the formula $-R_aR_b$ where R_a is an alkyl radical as defined above and R_b is one or more aryl radicals as defined above, *e.g.*, benzyl, diphenylmethyl and the like. The aryl radical(s) may be optionally substituted as described above.

"Aralkenyl" refers to a radical of the formula $-R_cR_b$ where R_c is an alkenyl radical as defined above and R_b is one or more aryl radicals as defined above, which may be optionally substituted as described above.

"Alkylene" and "alkylene chain" refer to a straight or branched divalent hydrocarbon chain, linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to seven carbon atoms, *e.g.*, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain may be attached to the rest of the molecule and to the radical group can be through any two carbons within the chain.

"Alkenylene" and "alkenylene chain" refer to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one double bond and having from two to seven carbon atoms, *e.g.*, ethenylene, propenylene, *n*-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and

to the radical group through a double bond or a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through any two carbons within the chain.

"Alkylidene" refers to a straight or branched hydrocarbon radical group consisting solely of carbon and hydrogen, containing at least one double bond, having from one to seven carbon atoms, and that is attached to the rest of the molecule through a double bond, *e.g.*, methylene, ethylidene, propylidene, *n*-butylidene, and the like.

"Cycloalkyl" refers to a stable monocyclic or bicyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, having from three to ten carbon atoms, and which is saturated and attached to the rest of the molecule by a single bond, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decalinyl and the like. Unless otherwise stated specifically in the specification, the term "cycloalkyl" is meant to include cycloalkyl radicals which are optionally substituted by one or more substituents independently selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, $-R^8-OR^7$, $-R^8-N(R^7)_2$, $-R^8-C(O)R^7$, $-R^8-C(O)OR^7$, $-R^8-C(O)N(R^7)_2$, $-R^8-N(R^9)C(O)OR^9$, $-R^8-N(R^9)C(O)R^9$, $-R^8-N(R^9)(S(O)_tR^9)$ (where t is 1 to 2), $-R^8-S(O)_pOR^9$ (where p is 1 to 2), $-R^8-S(O)_tR^9$ (where t is 0 to 2), and $-R^8-S(O)_pN(R^9)_2$ (where p is 1 to 2) where each R^7, R^8 and R^9 is as defined above in the Summary of the Invention.

"Cycloalkylalkyl" refers to a radical of the formula $-R_aR_d$ where R_a is an alkyl radical as defined above and R_d is a cycloalkyl radical as defined above. The alkyl radical and the cycloalkyl radical may be optionally substituted as defined above.

"Halo" refers to bromo, chloro, fluoro or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like.

"Haloalkenyl" refers to an alkenyl radical, as defined above, that is

substituted by one or more halo radicals, as defined above, *e.g.*, 2-bromoethenyl, 3-bromoprop-1-enyl, and the like.

"Haloalkylidene" refers to an alkylidene radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, difluoromethylene, dichloromethylene, and the like.

"Heterocyclyl" refers to a stable 3- to 18-membered non-aromatic ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purposes of this invention, the heterocyclyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone. Unless stated otherwise specifically in the specification, the term "heterocyclyl" is meant to include heterocyclyl radicals as defined above which are optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, $-R^8-OR^7$, $-R^8-N(R^7)_2$, $-R^8-C(O)R^7$, $-R^8-C(O)OR^7$, $-R^8-C(O)N(R^7)_2$, $-R^8-N(R^9)C(O)OR^9$, $-R^8-N(R^9)C(O)R^9$, $-R^8-N(R^9)(S(O)_tR^9)$ (where t is 1 to 2), $-R^8-S(O)_pOR^9$ (where p is 1 to 2), $-R^8-S(O)_tR^9$ (where t is 0 to 2), and $-R^8-S(O)_pN(R^9)_2$ (where p is 1 to 2) where each R^7, R^8 and R^9 is as defined above in the Summary of the Invention.

"Heterocyclylalkyl" refers to a radical of the formula $-R_aR_e$ where R_a is an alkyl radical as defined above and R_e is a heterocyclyl radical as defined above, and if the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkyl radical at the nitrogen atom. The heterocyclyl radical may be optionally

substituted as defined above.

"Heteroaryl" refers to a 3- to 18-membered aromatic ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purposes of this invention, the heterocyclyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzthiazolyl, benzindolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, indolizinyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl. Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, $-R^8-OR^7$, $-R^8-N(R^7)_2$, $-R^8-C(O)R^7$, $-R^8-C(O)OR^7$, $-R^8-C(O)N(R^7)_2$, $-R^8-N(R^9)C(O)OR^9$, $-R^8-N(R^9)C(O)R^9$, $-R^8-N(R^9)(S(O)_tR^9)$ (where t is 1 to 2), $-R^8-S(O)_pOR^9$ (where p is 1 to 2), $-R^8-S(O)_tR^9$ (where t is 0 to 2), and $-R^8-S(O)_pN(R^9)_2$ (where p is 1 to 2) where each R^7, R^8 and R^9 is as defined above in the Summary of the Invention.

"Heteroarylalkyl" refers to a radical of the formula $-R_aR_f$ where R_a is an alkyl radical as defined above and R_f is a heteroaryl radical as defined above. The heteroaryl radical may be optionally substituted as defined above.

"Heteroarylalkenyl" refers to a radical of the formula $-R_bR_f$ where R_b is an

alkenyl radical as defined above and R_f is a heteroaryl radical as defined above. The heteroaryl radical may be optionally substituted as defined above.

As used herein, compounds which are "commercially available" may be obtained from standard commercial sources including Acros Organics (Pittsburgh PA), Aldrich Chemical (Milwaukee WI; including Sigma Chemical and Fluka), American Tissue Culture Collection (ATCC, Rockville, MD), Apin Chemicals Ltd. (Milton Park UK), Avocado Research (Lancashire U.K.), BDH Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chemservice Inc. (West Chester PA), Crescent Chemical Co. (Hauppauge NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester NY), EM Industries, Inc. (Hawthorne, NY; World Wide Web), Fisher Scientific Co. (Pittsburgh PA), Fisher Scientific Co. (Hampton, NH), Fisons Chemicals (Leicestershire UK), Frontier Scientific (Logan UT), ICN Biomedicals, Inc. (Costa Mesa CA), Key Organics (Cornwall U.K.), Lancaster Synthesis (Windham NH; www.lancaster.co.uk), Maybridge Chemical Co. Ltd. (Cornwall U.K.), Parish Chemical Co. (Orem UT), Pfaltz & Bauer, Inc. (Waterbury CN), Polyorganix (Houston TX), Pierce Chemical Co. (Rockford IL), Praxair (Vancouver, B.C.), Riedel de Haen AG (Hannover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), Steraloids Inc. (Newport, RI), TCI America (Portland OR), Trans World Chemicals, Inc. (Rockville MD), and Wako Chemicals USA, Inc. (Richmond VA).

As used herein, "suitable conditions" for carrying out a synthetic step are explicitly provided herein or may be discerned by reference to publications directed to methods used in synthetic organic chemistry. The reference books and treatise set forth above that detail the synthesis of reactants useful in the preparation of compounds of the present invention, will also provide suitable conditions for carrying out a synthetic step according to the present invention.

As used herein, "methods known to one of ordinary skill in the art" may be identified through various reference books and databases. Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds of the present invention, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New

York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Specific and analogous reactants may also be identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C., may be contacted for more details). Chemicals that are known but not commercially available in catalogs may be prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the present invention is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

As used herein, the term C_{1-30} organic moiety refers to a stable arrangement of atoms composed of at least one and not more than about the maximum carbon number set forth in the range, typically not more than about 30 carbon atoms, and any number of non-carbon atoms.

The C_{1-30} organic moiety may be a saturated or unsaturated hydrocarbyl radical. A saturated hydrocarbyl radical is defined according to the present invention as any radical composed exclusively of carbon and hydrogen, where single bonds are exclusively used to join carbon atoms together. Thus, any stable arrangement of carbon and hydrogen atoms, having at least one carbon atom, is included within the scope of a saturated hydrocarbon radical according to the invention. Some specific terminology that may be used to refer to specific carbon atom arrangements will be discussed below.

The carbon atoms may form an alkyl group as defined herein. The carbon atoms may form a cycloalkyl group as defined herein. Additional groups within the scope of "cycloalkyl" as defined herein are polycycloalkyl groups, defined below.

A polycycloalkyl group is an arrangement of carbon atoms wherein at least

one carbon atom is a part of at least two separately identifiable rings. The polycycloalkyl group may contain bridging between two carbon atoms, where bicyclo[1.1.0]butyl, bicyclo[3.2.1]octyl, bicyclo[5.2.0]nonyl, tricycl[2.2.1.0[1]]heptyl, norbornyl and pinanyl are representative examples. The polycycloalkyl group may contain one or more fused ring systems, where decalinyl (radical from decalin) and perhydroanthracenyl are representative examples. The polycycloalkyl group may contain a spiro union, in which a single atom is the only common member of two rings. Spiro[3.4]octyl, spiro[3.3]heptyl and spiro[4.5]decyl are representative examples.

In addition, the saturated hydrocarbyl radical can be composed of any combination of two or more of the above, *i.e.*, any combination of alkyl and cycloalkyl groups. Thus, the C_{1-30} organic moiety may be an alkyl group (*e.g.*, methyl) with a cycloalkyl (*e.g.*, cyclohexyl) substituent, so that C_{1-30} organic moiety is a cyclohexylmethyl group. As another example, the C_{1-30} organic moiety may be a cycloalkyl group (*e.g.*, cyclooctyl) having two alkyl substituents (*e.g.*, a methyl and ethyl substituent), so that the C_{1-30} organic moiety is a methylethylcyclooctyl group. As a final example, the C_{1-30} organic moiety may be a cycloalkyl group with an alkyl substituent, where the alkyl substituent is substituted with a polycycloalkyl substituent.

As indicated above, the C_{1-30} organic moiety may be an unsaturated hydrocarbyl radical. Such an C_{1-30} organic moiety is defined as having a carbon arrangement as set forth above for saturated hydrocarbyl radicals, with the additional feature that at least one bond between any two carbon atoms is other than a single bond. An alkyl group containing at least one single double bond is referred to herein as an alkenyl group. An alkyl group containing at least one triple bond is referred herein to as an alkynyl group.

Likewise, the cycloalkyl group may have one or more double or triple bonds, and be included within the scope of an unsaturated hydrocarbyl radical according to the invention. Cycloalkenyl and cycloalkynyl are general names given to groups having a single carbon-based ring with a single double and triple bond in the ring, respectively. Cycloalkadienyl groups are cycloalkyl groups with two double bonds contained in the ring structure. The double bond may be exocyclic to the ring, *e.g.*, a

carbon atom of the ring may have a $=CH_2$ group (*i.e.*, a methylidene group) or higher homologue bonded to it.

A ring may be unsaturated to the extent of being aromatic, and still be included within the scope of an unsaturated hydrocarbyl radical. Thus, an aryl group as defined herein is included within the scope of such hydrocarbyl groups. As any combination of the above is also included within the scope of an unsaturated hydrocarbyl radical, aralkyl (C_{1-30} organic moiety is an alkyl group with at least one aryl substituent, *e.g.*, benzyl) and alkylaryl (C_{1-30} organic moiety is an aryl ring with at least one alkyl substituent, *e.g.*, tolyl) groups are included within the scope of C_{1-30} organic moiety. C_6 aryls are a preferred component of organic moieties of the invention.

Also included within the scope of an C_{1-30} organic moiety are those organic moieties that contain one or more heteroatoms. Heteroatoms according to the invention are any atom other than carbon and hydrogen. A preferred class of heteroatoms are naturally occurring atoms (other than carbon and hydrogen). Another preferred class are non-metallic (other than carbon and hydrogen). Another preferred class consists of boron, nitrogen, oxygen, phosphorous, sulfur, selenium and halogen (*i.e.*, fluorine, chlorine, bromine and iodine, with fluorine and chlorine being preferred). Another preferred class consists of nitrogen, oxygen, sulfur and halogen. Another preferred class consists of nitrogen, oxygen and sulfur. Oxygen is a preferred heteroatom. Nitrogen is a preferred heteroatom.

For example, the C_{1-30} organic moiety may be a hydrocarbyl radical as defined above, with at least one substituent containing at least one heteroatom. In other words, the C_{1-30} organic moiety may be a hydrocarbyl radical as defined above, wherein at least one hydrogen atom is replaced with a heteroatom. For example, if the heteroatom is oxygen, the substituent may be a carbonyl group, *i.e.*, two hydrogens on a single carbon atom are replaced by an oxygen, to form either a ketone or aldehyde group. Alternatively, one hydrogen may be replaced by an oxygen atom, in the form of an hydroxy, alkoxy, aryloxy, aralkyloxy, alkylaryloxy (where alkoxy, aryloxy, aralkyloxy, alkylaryloxy may be collectively referred to as hydrocarbyloxy), heteroaryloxy, -OC(O)R, ketal, acetal, hemiketal, hemiacetal, epoxy and $-OSO_3M$. The heteroatom may be a

halogen. The heteroatom may be a nitrogen, where the nitrogen forms part of an amino ($-NH_2$, -NHR, $-N(R)_2$), alkylamido, arylamido, arylalkylamido, alkylarylamido, nitro, $-N(R)SO_3M$ or aminocarbonylamide group. The heteroatom may be a sulfur, where the sulfur forms part of a thiol, thiocarbonyl, $-SO_3M$, sulfonyl, sulfonamide or sulfonhydrazide group. The heteroatom may be part of a carbon-containing substituent such as formyl, cyano, -C(O)OH, -C(O)OR, -C(O)OM, -C(O)R, $-C(O)N(R)_2$, carbamate, carbohydrazide and carbohydroxamic acid.

In the above exemplary heteroatom-containing substituents, R represents the remainder of the C_{1-30} organic moiety and M represents proton or a metal ion. Preferred metal ions, in combination with a counterion, form physiologically tolerated salts. A preferred metal from which a metal ion may be formed include an alkali metal [for example, lithium (Li), sodium (Na), potassium (K), rubidium (Rb) and cesium (Cs)] an alkaline earth metal (for example, magnesium (Mg), calcium (Ca) and strontium (Sr)], or manganese (Mn), iron (Fe), zinc (Zn) or silver (Ag). An alkali metal or an alkaline earth metal are preferred M groups. Sodium, potassium, magnesium and calcium are preferred M groups. Sodium and potassium are preferred M groups.

Another class of C_{1-30} organic moieties according to the invention are hydrocarbyl radicals as defined above, wherein at least one heteroatom is substituted for a carbon atom in the hydrocarbyl. One example of such organic moieties is the heterocyclyls defined herein. Another example of such organic moieties have a heteroatom bridging (a) the radical to which the organic moiety is bonded and (b) the remainder of the organic moiety. Examples include alkoxy, aryloxy, aralkoxy and alkylaryloxy radicals, which may collectively be referred to herein as hydrocarbyloxy radicals or moieties. Thus, -OR is an exemplary C_{1-30} organic moiety of the invention (where R is the remainder of the C_{1-30} organic moiety). Another example is -NHR (where R is the remainder of the C_{1-30} organic moiety). Other examples include $-R^8-OR^7$ and $-R^8-N(R^7)_2$ where R^7 and R^8 are as defined above in the Summary of the Invention and R^{10} is a bond or a straight or branched alkylene or alkenylene chain.

While the C_{1-30} organic moiety may have up to about 30 carbon atoms, preferred organic moieties of the invention have fewer than 30 carbon atoms, for

example, up to about 25 carbon atoms, more preferably up to about 20 carbon atoms. The organic moiety may have up to about 15 carbon atoms, or up to about 12 or 10 carbon atoms. A preferred category of organic moieties has up to about 8 or 6 carbon atoms.

"Prodrugs" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound of the invention. Thus, the term "prodrug" refers to a metabolic precursor of a compound of the invention that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject in need thereof, but is converted in vivo to an active compound of the invention. Prodrugs are typically rapidly transformed in vivo to yield the parent compound of the invention, for example, by hydrolysis in blood. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam).

A discussion of prodrugs is provided in Higuchi, T., *et al.*, "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

The term "prodrug" is also meant to include any covalently bonded carriers which release the active compound of the invention in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of the invention may be prepared by modifying functional groups present in the compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound of the invention. Prodrugs include compounds of the invention wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the compound of the invention is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the invention and the like.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from

a reaction mixture, and formulation into an efficacious therapeutic agent.

"Mammal" includes humans and domestic animals, such as cats, dogs, swine, cattle, sheep, goats, horses, rabbits, and the like.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

"Oxygen protecting group" refers to a radical which protects and maintains a hydroxy group during subsequent chemical reactions. Such groups include, but are not limited to, trialkylsilyl or diarylalkylsilyl (*e.g.*, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art and as described herein. The use of protecting groups, particularly oxygen protecting groups, is described in detail in Green, T.W. and P.G.M. Wutz, Protective Groups in Organic Synthesis (1991), 2nd Ed., Wiley-Interscience.

"Leaving group initiator" refers to a radical which, together with the oxygen to which is it attached, forms a leaving group which is easily removed from the rest of the molecule upon attack by the appropriate nucleophile. The hydroxy radical is not a good leaving group and must therefore be converted to a group that does leave. One way is to protonate the hydroxy radical (to form a more acidic leaving group). Another is to convert the hydroxy to a reactive ester, most commonly, to a sulfonic ester. The sulfonic ester groups tosylate, brosylate, nosylate and mesylate are frequently used. Other leaving groups include oxonium ions, alkyl perchorates, ammonioalkanesulfonate esters, alkyl fluorosulfonates and the fluorinated compounds triflates and nonaflates.

"Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the

United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring

substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

"Therapeutically effective amount" refers to that amount of a compound of the invention which, when administered to a mammal, preferably a human, is sufficient to effect treatment, as defined below, of inflammatory disease in the mammal. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the condition and its severity, and the age of the mammal to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

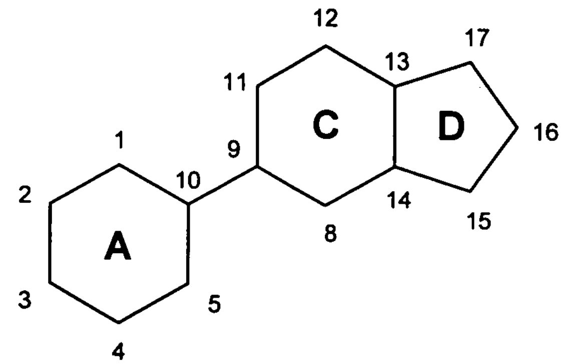
"Treating" or "treatment" as used herein covers the treatment of the disease or condition of interest in a mammal, preferably a human, having the disease or disorder of interest, and includes:

(i) preventing the disease or condition from occurring in a mammal, in particular, when such mammal is predisposed to the condition but has not yet been diagnosed as having it;

(ii) inhibiting the disease or condition, *i.e.*, arresting its development; or

(iii) relieving the disease or condition, *i.e.*, causing regression of the disease or condition.

Compounds of the invention have a central nucleus of three rings, designated herein as A, C, and D as shown below:



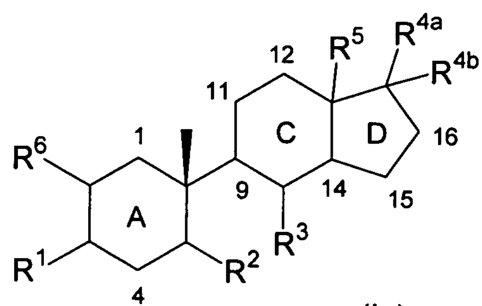
The carbons of the central nucleus are numbered as set forth above. For purposes herein, the carbon at position 1 of the central nucleus is indicated herein as C1, and so forth.

In the compounds of the invention, unless otherwise indicated, each of rings A, C, and D is independently fully saturated, partially saturated or fully unsaturated. That is, hydrogens attached to any of the carbons at positions 1-5 and 8-17 may be omitted so as to allow unsaturation within the A, C and/or D rings. For example, when carbons at numerals 5, 8, 9, 10, 13 and 14 are indicated as being substituted with one hydrogen, and it is also indicated that each of rings A, C and D is independently fully saturated, partially saturated or fully unsaturated, then any one or more of the hydrogens attached to carbons at numerals 5, 8, 9 and 14 may be omitted in order to allow unsaturation at the carbon atom.

The compounds of the invention, or their pharmaceutically acceptable salts may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be

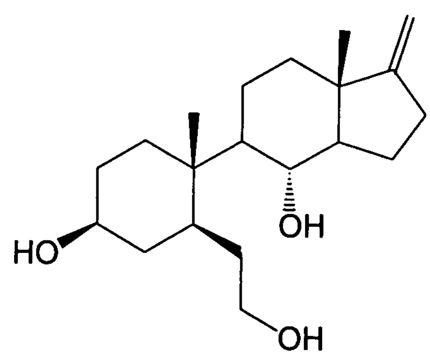
included.

The nomenclature used herein for the compounds of the invention is a modified form of the I.U.P.A.C. nomenclature system wherein the compounds are named herein as derivatives of the indene moiety. The locant numbering of the various substituents off the indene ring in the names of the compounds of the invention is based on the standard locant numbering system for indene rings. In addition, the configuration of the substituents are indicated in the names of the compounds by an "α" if the substituent is below the plane of the indene ring and by a "β" is the substituent is above the plane of the indene ring. For example, a compound of formula (Ia) (showing the numbering of the *carbons*:



(Ia)

where C1, C4, C11, C12, C15 and C16 are each independently substituted with two hydrogens; C9 and C14 are each independently substituted with hydrogen; R^1 is β-hydroxy; R^2 is β-(2-hydroxyethyl); R^3 is α-hydroxy; R^{4a} and R^{4b} together form methylene; R^5 is β-methyl; and R^6 is hydrogen, *i.e.*, a compound of the following formula:



is named herein as 5-(1β-methyl-4β-hydroxy-2β-(2-hydroxyethyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene.

The compounds of the invention may, and typically do, exist as solids,

including crystalline solids which can be crystallized from common solvents such as ethanol, *N,N*-dimethylformamide, water, or the like or mixtures thereof. The crystallization process may, depending on the crystallization conditions, provide various polymorphic structures. Typically, a more thermodynamically stable polymorph is advantageous to the commercial scale manufacture of a steroid compound of the invention, and is a preferred form of the compound.

Often, crystallizations produce a solvate of the compound of the invention. As used herein, the term "solvate" refers to an aggregate that comprises one or more compounds of the invention with one or more molecules of solvent. The solvent may be water, in which case the solvate may be a hydrate. Alternatively, the solvent may be an organic solvent. Thus, the compounds of the present invention may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. The compound of the invention may be true solvates, while in other cases, the compound of the invention may merely retain adventitious water or solvent or a mixture of water and solvent.

As used herein, a "pharmaceutically acceptable solvate" refers to a solvate that retains the biological effectiveness and properties of the biologically active compounds of the invention. Examples of pharmaceutically acceptable solvates include, but are not limited to, water, isopropanol, ethanol, methanol, DMSO, EtOAc, acetic acid, and ethanolamine. It should be appreciated by those skilled in the art that solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Sykes, P. A., *Guidebook to Mechanism in Organic Chemistry*, 6th Ed (1986, John Wiley & Sons, N.Y.) is an exemplary reference that describe solvates.

B. <u>Pharmaceutical Compositions</u>

The present invention provides a pharmaceutical or veterinary composition (hereinafter, collectively referred to as a pharmaceutical composition) containing a compound of the invention as described above, in admixture with a

pharmaceutically acceptable carrier. The invention further provides a composition, preferably a pharmaceutical composition, containing an effective amount of a compound as described above, in association with a pharmaceutically acceptable carrier.

The pharmaceutical compositions of the present invention may be in any form which allows for the composition to be administered to a patient. For example, the composition may be in the form of a solid, liquid or gas (aerosol). Typical routes of administration include, without limitation, oral, topical, parenteral, sublingual, rectal, vaginal, ocular, and intranasal. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. Pharmaceutical composition of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the composition to a patient. Compositions that will be administered to a patient take the form of one or more dosage units, where for example, a tablet may be a single dosage unit, and a container of a compound of the invention in aerosol form may hold a plurality of dosage units.

Materials used in preparing the pharmaceutical compositions should be pharmaceutically pure and non-toxic in the amounts used. It will be evident to those of ordinary skill in the art that the optimal dosage of the active ingredient(s) in the pharmaceutical composition will depend on a variety of factors. Relevant factors include, without limitation, the type of subject (*e.g.*, human), the particular form of the active ingredient, the manner of administration and the composition employed.

In general, the pharmaceutical composition includes an (where "a" and "an" refers here, and throughout this specification, as one or more) active compound of the invention as described herein, in admixture with one or more carriers. The carrier(s) may be particulate, so that the compositions are, for example, in tablet or powder form. The carrier(s) may be liquid, with the compositions being, for example, an oral syrup or injectable liquid. In addition, the carrier(s) may be gaseous, so as to provide an aerosol composition useful in, *e.g.*, inhalatory administration.

When intended for oral administration, the composition is preferably in either solid or liquid form, where semi-solid, semi-liquid, suspension and gel forms are

included within the forms considered herein as either solid or liquid.

As a solid composition for oral administration, the composition may be formulated into a powder, granule, compressed tablet, pill, capsule, chewing gum, wafer or the like form. Such a solid composition will typically contain one or more inert diluents or edible carriers. In addition, one or more of the following adjuvants may be present: binders such as carboxymethylcellulose, ethyl cellulose, microcrystalline cellulose, or gelatin; excipients such as starch, lactose or dextrins, disintegrating agents such as alginic acid, sodium alginate, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin, a flavoring agent such as peppermint, methyl salicylate or orange flavoring, and a coloring agent.

When the composition is in the form of a capsule, *e.g.*, a gelatin capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol, cyclodextrin or a fatty oil.

The composition may be in the form of a liquid, *e.g.*, an elixir, syrup, solution, emulsion or suspension. The liquid may be for oral administration or for delivery by injection, as two examples. When intended for oral administration, preferred composition contain, in addition to the present compounds, one or more of a sweetening agent, preservatives, dye/colorant and flavor enhancer. In a composition intended to be administered by injection, one or more of a surfactant, preservative, wetting agent, dispersing agent, suspending agent, buffer, stabilizer and isotonic agent may be included.

The liquid pharmaceutical compositions of the invention, whether they be solutions, suspensions or other like form, may include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, cyclodextrin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic

acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Physiological saline is a preferred adjuvant. An injectable pharmaceutical composition is preferably sterile.

A liquid composition intended for either parenteral or oral administration should contain an amount of a compound of the invention such that a suitable dosage will be obtained. Typically, this amount is at least 0.01% of a compound of the invention in the composition. When intended for oral administration, this amount may be varied to be between 0.1% and about 80% of the weight of the composition. Preferred oral compositions contain between about 4% and about 50% of the active compound of the invention. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.01% to 2% by weight of active compound.

The pharmaceutical composition may be intended for topical administration, in which case the carrier may suitably comprise a solution, emulsion, ointment or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, beeswax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers. Thickening agents may be present in a pharmaceutical composition for topical administration. If intended for transdermal administration, the composition may include a transdermal patch or iontophoresis device. Topical formulations may contain a concentration of the compound of formula the invention of from about 0.01% to about 10% w/v (weight per unit volume).

The composition may be intended for rectal administration, in the form, *e.g.*, of a suppository which will melt in the rectum and release the drug. The composition for rectal administration may contain an oleaginous base as a suitable nonirritating excipient. Such bases include, without limitation, lanolin, cocoa butter and polyethylene glycol.

The composition may include various materials which modify the physical

form of a solid or liquid dosage unit. For example, the composition may include materials that form a coating shell around the active ingredients. The materials which form the coating shell are typically inert, and may be selected from, for example, sugar, shellac, and other enteric coating agents. Alternatively, the active ingredients may be encased in a gelatin capsule.

The composition in solid or liquid form may include an agent which binds to the active component(s) and thereby assists in the delivery of the active components. Suitable agents which may act in this capacity include a monoclonal or polyclonal antibody, a protein or a liposome.

The pharmaceutical composition of the present invention may consist of gaseous dosage units, *e.g.*, it may be in the form of an aerosol. The term aerosol is used to denote a variety of systems ranging from those of colloidal nature to systems consisting of pressurized packages. Delivery may be by a liquefied or compressed gas or by a suitable pump system which dispenses the active ingredients. Aerosols of compounds of the invention may be delivered in single phase, bi-phasic, or tri-phasic systems in order to deliver the active ingredient(s). Delivery of the aerosol includes the necessary container, activators, valves, subcontainers, spacers and the like, which together may form a kit. Preferred aerosols may be determined by one skilled in the art, without undue experimentation.

Whether in solid, liquid or gaseous form, the pharmaceutical composition of the present invention may contain one or more known pharmacological agents used in the treatment of inflammation (including asthma, allergy, rheumatoid arthritis, multiple sclerosis, etc.), autoimmune diseases (including diabetes and lupus erythematosus), and proliferative disorders (cancers).

The pharmaceutical compositions may be prepared by methodology well known in the pharmaceutical art.

A composition intended to be administered by injection can be prepared by combining the compound of the invention with water so as to form a solution. A surfactant may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the

compound of the invention so as to facilitate dissolution or homogeneous suspension of the active compound in the aqueous delivery system.

C. Methods of Use

The compounds of the invention, or pharmaceutical compositions comprising one of more of these compounds and a pharmaceutically acceptable carrier, diluent or excipient, may be used in a method for treating or preventing an inflammatory condition or disease in a patient, where the method comprises administering to the patient in need thereof an amount of a compound or composition according to the present invention, where the amount is effective to treat or prevent the inflammatory condition or disease of the patient.

The inflammatory condition or disease may involve acute or chronic inflammation of bone and/or cartilage of joints; the inflammatory condition or disease may be an arthritis selected from rheumatoid arthritis, gouty arthritis or juvenile rheumatoid arthritis; the inflammatory condition may be an autoimmune condition or disease; the inflammatory condition or disease may involve central nervous system inflammation (*e.g.*, wherein the central nervous system disease is multiple sclerosis, or wherein the central nervous system disease is Alzheimer's); the inflammatory condition or disease may be lupus erythematosus disease; the inflammatory condition or disease may be an inflammatory bowel disease (*e.g.*, Crohn's disease or ulcerative colitis); the inflammatory condition or disease may be an inflammatory cutaneous disease (*e.g.*, psoriasis or dermatitis); the inflammatory condition or disease may be graft *vs* host disease; the inflammatory condition or disease may be vascular (*e.g.*, vasculitis); the inflammatory condition or disease may be an atherosclerotic disease; the inflammatory condition or disease may involve respiratory inflammation (*e.g.*, wherein the respiratory disease is asthma, or wherein the respiratory disease is chronic obstructive pulmonary disease; or wherein the respiratory disease is emphysema); the inflammatory condition or disease may be pulmonary sarcadosis; the inflammatory condition or disease may be ocular inflammation or allergy; the inflammatory condition or disease may be allergic rhinitis; the condition or disease may be associated with leukocyte infiltration; the

condition or disease may be associated with edema; the condition or disease may be associated with ischemia reperfusion injury; the condition or disease may be associated with elevated levels of inflammatory cytokines (*e.g.*, wherein the inflammatory cytokine is IL-1, or wherein the inflammatory cytokine is IL-2, or wherein the inflammatory cytokine is IL-3, or wherein the inflammatory cytokine is interleukin (IL)-4, or wherein the inflammatory cytokine is IL-5, or wherein the inflammatory cytokine is IL-6, or wherein the inflammatory cytokine is IL-8, or wherein the inflammatory cytokine is IL-9, or wherein the inflammatory cytokine is IL-10, or wherein the inflammatory cytokine is IL-12, or wherein the inflammatory cytokine is IL-13, or wherein the inflammatory cytokine is IL-18, or wherein the inflammatory cytokine is TNF-α, or wherein the inflammatory cytokine is TGF-β, or wherein the inflammatory cytokine is GM-CSF, or wherein the inflammatory cytokine is IFN-γ, or wherein the inflammatory cytokine is LTB4, or wherein the inflammatory cytokine is a member of the cysteinyl leukotriene family, or wherein the inflammatory cytokine is regulated on activation normal T cell expressed and secreted (RANTES), or wherein the inflammatory cytokine is eotaxin-1, 2, or 3, or wherein the inflammatory cytokine is macrophage inflammatory protein (MIP)-1α, or wherein the inflammatory cytokine is monocyte chemoattractant protein-1, 2, 3, or 4); the condition or disease may be associated with altered levels of inflammatory adhesion molecules (*e.g.*, wherein the adhesion molecule is an immunoglobulin such as vascular cell adhesion molecule (VCAM-1 or 2) or intercellular adhesion molecule (ICAM-1 or 2); wherein the adhesion molecule is an integrin such as very late antigen-4 (VLA-4) or Mac-1; wherein the adhesion molecule is a selectin such as e-selectin).

Furthermore, the present invention provides a method for treating or preventing a disease or condition in a patient, where the disease or condition is associated with pathological conditions that involve leukocyte infiltration, the method comprising administering to a patient in need thereof an amount of a compound or a composition of the present invention, wherein the amount is effective to treat or prevent a disease or condition associated with pathological conditions that involve leukocyte infiltration.

Furthermore, the present invention provides a method of treating or preventing arthritis in a patient, comprising administering to a patient in need thereof an amount of a compound or composition of the present invention, where the amount is effective to treat or prevent arthritis in the patient.

Furthermore, the present invention provides a method of treating or preventing inflammatory bowel disease in a patient, comprising administering to a patient in need thereof an amount of a compound or composition of the present invention, where the amount is effective to treat or prevent inflammatory bowel disease in the patient.

Furthermore, the present invention provides a method of treating or preventing inflammatory bowel disease in a patient, comprising administering to a patient in need thereof an amount of a compound or composition of the present invention, where the amount is effective to treat or prevent psoriasis in the patient.

Furthermore, the present invention provides a method of treating or preventing atherosclerosis in a patient, comprising administering to a patient in need thereof an amount of a compound or composition of the present invention, where the amount is effective to treat or prevent atherosclerosis in the patient.

In a method of the present invention, a compound of the invention, or a pharmaceutical composition comprising one or more compounds of the invention and a pharmaceutically acceptable carrier, diluent or excipient, may, although need not, achieve one or more of the following desired results in the subject to whom has been administered a compound of the invention as defined above, or a composition containing one of these compounds and a pharmaceutically acceptable carrier, diluent or excipient:

1. Inhibition of leukocyte infiltration (*e.g.*, neutrophils, macrophages, etc.)
2. Inhibition of leukocyte activation
3. Alteration of lymphocyte ratio (*e.g.*, TH1 vs TH2 cells)
4. Inhibition of leukocyte chemotaxis;
5. Inhibition of TNF-α production and/or release;

6. Inhibition of chemokine production and/or release (*e.g.*, eotaxin, etc.);
7. Inhibition of adhesion molecule production, release and/or function (*e.g.* VCAM, VLA–4, etc.);
8. Inhibition of edema;
9. Inhibition of interleukin cytokine production and/or release (e.g., IL-1, IL-2, IL-3, IL-4, IL-5, IL6, IL-8, IL-9, IL10, IL-12, IL-13, IL-18);
10. Inhibition of inflammatory mediator release (*e.g.*, leukotrienes, tryptase, adenosine etc.);
11. Inhibition of parameters of arthritis;
12. Inhibition of parameters of inflammatory bowel disease;
13. Inhibition of parameters of psoriasis;
14. Inhibition of parameters of atherosclerosis.

The compounds of the invention disclosed herein or pharmaceutical or compositions comprising one of more of these compounds and a pharmaceutically acceptable carrier, diluent or excipient, may be used in a method for treating or preventing a proliferative disorder in a patient, where the method comprises administering to the patient in need thereof an amount of a compound or composition according to the present invention, where the amount is effective to treat or prevent the proliferative disorder of the patient. As used herein, proliferative disorders includes, without limitation, all leukemias and solid tumors that are susceptible to undergoing differentiation or apoptosis upon interruption of their cell cycle.

Thus, the inventive method may be used to treat inflammation, including both acute and chronic inflammation, as well as certain proliferative disorders (cancers). As used herein, inflammation includes, without limitation, arthritis (where this term encompasses over 100 kinds of diseases, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, osteoarthritis, gout, and synovitis), inflammations of the brain (including multiple sclerosis, Alzheimer's, AIDS dementia, stroke, encephalitis, trauma, and Creutzfeld-Jakob disease), inflammatory bowel disease (including Crohn's disease and ulcerative colitis), irritable bowel syndrome, ischemia-reperfusion injury

including myocardial infarction, sarcoidosis, psoriasis, tissue/organ transplant, graft *vs* host disease, systemic lupus erythematosus, Type I juvenile diabetes, vasculitis, artherosclerosis, cardiomyopathy, autoimmune myocarditis, atopic dermatitis, asthma, allergy, allergic rhinitis, and chronic obstructive pulmonary disease (including emphysema and bronchitis).

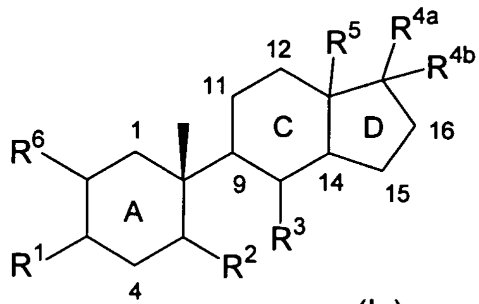
The inventive method provides for administering a therapeutically effective amount of a compound of the invention, including salts, compositions etc. thereof. As used herein, the actual amount encompassed by the term "therapeutically effective amount" will depend on the route of administration, the type of warm-blooded animal being treated, and the physical characteristics of the specific warm-blooded animal under consideration. These factors and their relationship to determining this amount are well known to skilled practitioners in the medical arts. This amount and the method of administration can be tailored to achieve optimal efficacy but will depend on such factors as weight, diet, concurrent medication and other factors that those skilled in the medical arts will recognize.

A therapeutically effective amount of a compound or pharmaceutical composition of the present invention will be sufficient to treat inflammation or proliferative diseases in a warm-blooded animal, such as a human. Methods of administering therapeutically effective amounts of anti-inflammatory agents are well known in the art and include the administration of inhalation, oral or parenteral forms. Such dosage forms include, but are not limited to, parenteral solutions, tablets, capsules, sustained release implants and transdermal delivery systems; or inhalation dosage systems employing dry powder inhalers or pressurized multi-dose inhalation devices.

The dosage amount and frequency are selected to create a therapeutically effective level of the agent without harmful effects. It will generally range from a dosage of about 0.001 to 100 mg/Kg/day, and typically from about 0.01 to 10 mg/Kg/day where administered orally or intravenously. Also, the dosage range will be typically from about 0.0001 to 10 mg/Kg/day where administered intranasally or by inhalation.

D. Preferred Embodiments of the Invention

Of the compounds of formula (I) set forth above in the Summary of the Invention, a preferred group of compounds are those compounds of formula (Ia):



(Ia)

wherein:

the A, C or D ring is independently fully saturated or partially saturated;

C1, C4, C11, C12, C15 and C16 are each independently substituted with two hydrogens;

C9 and C14 are each independently substituted with hydrogen;

R^1 is $-OR^7$ or $-N(R^7)_2$;

R^2 and R^3 are each independently selected from the group consisting of $-R^8-OR^7$, $-R^8-OC(O)R^9$, $-R^{10}-N(R^7)_2$, $-R^{10}-N(R^9)C(O)R^9$, $-R^{10}-N(R^9)S(O)_tR^9$ (where t is 1 or 2), $-R^{10}-N(R^9)C(NR^9)N(R^9)_2$, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, and optionally substituted heteroarylalkenyl;

R^{4a} and R^{4b} are each independently selected from hydrogen, alkyl, alkenyl or alkynyl;

or R^{4a} is hydrogen, alkyl, alkenyl or alkynyl and R^{4b} is a direct bond to the carbon at C16;

or R^{4a} and R^{4b} together form alkylidene or haloalkylidene;

R^5 is alkyl or R^5 is a direct bond to the carbon at C14;

R^6 is hydrogen, $-R^8-OR^7$ or $-R^8-N(R^7)_2$;

each R^7 is independently selected from the group consisting of hydrogen,

$-R^{10}-OR^9$, $-R^{10}-N(R^9)_2$, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

each R^8 is independently selected from the group consisting of a direct bond, a straight or branched alkylene chain, and a straight or branched alkenylene chain; and

each R^9 is independently selected from the group consisting of hydrogen, alkyl, aryl and aralkyl;

each R^{10} is independently selected from the group consisting of a straight or branched alkylene and a straight or branched alkenylene chain.

Of this group of compounds, one preferred subgroup of compounds is the subgroup wherein:

R^1 is $-OR^7$;

R^2 and R^3 are each independently selected from the group consisting of $-R^8-OR^7$, $-R^8-OC(O)R^9$, $-R^{10}-N(R^7)_2$, $-R^{10}-N(R^9)C(O)R^9$, $-R^{10}-N(R^9)S(O)_tR^9$ (where t is 1 or 2), $-R^{10}-N(R^9)C(NR^9)N(R^9)_2$, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, and optionally substituted heteroarylalkenyl;

R^{4a} and R^{4b} are each independently selected from hydrogen, alkyl, alkenyl or alkynyl;

or R^{4a} is hydrogen, alkyl, alkenyl or alkynyl and R^{4b} is a direct bond to the carbon at C16;

or R^{4a} and R^{4b} together form alkylidene or haloalkylidene;

R^5 is alkyl or R^5 is a direct bond to the carbon at C14;

R^6 is hydrogen, $-R^8-OR^7$ or $-R^8-N(R^7)_2$;

each R^7 is independently selected from the group consisting of hydrogen, $-R^{10}-OR^9$, $-R^{10}-N(R^9)_2$, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally

substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

each R^8 is independently selected from the group consisting of a direct bond, a straight or branched alkylene chain, and a straight or branched alkenylene chain; and

each R^9 is independently selected from the group consisting of hydrogen, alkyl, aryl and aralkyl;

each R^{10} is independently selected from the group consisting of a straight or branched alkylene and a straight or branched alkenylene chain.

Of this subgroup of compounds, one preferred class of compounds is that class wherein:

R^1 is $-OR^7$;

R^2 is $-R^8-OR^7$;

R^3 is selected from the group consisting of $-R^8-OR^7$, $-R^8-OC(O)R^9$, $-R^{10}-N(R^7)_2$, $-R^{10}-N(R^9)C(O)R^9$, $-R^{10}-N(R^9)S(O)_tR^9$ (where t is 1 or 2), $-R^{10}-N(R^9)C(NR^9)N(R^9)_2$, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, and optionally substituted heteroarylalkenyl;

R^{4a} and R^{4b} are each independently selected from hydrogen, alkyl, alkenyl or alkynyl;

or R^{4a} is hydrogen, alkyl, alkenyl or alkynyl and R^{4b} is a direct bond to the carbon at C16;

or R^{4a} and R^{4b} together form alkylidene or haloalkylidene;

R^5 is alkyl or R^5 is a direct bond to the carbon at C14;

R^6 is hydrogen, $-R^8-OR^7$ or $-R^8-N(R^7)_2$;

each R^7 is independently selected from the group consisting of hydrogen, $-R^{10}-OR^9$, $-R^{10}-N(R^9)_2$, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted

heteroarylalkyl;

each R^8 is independently selected from the group consisting of a direct bond, a straight or branched alkylene chain, and a straight or branched alkenylene chain; and

each R^9 is independently selected from the group consisting of hydrogen, alkyl, aryl and aralkyl;

each R^{10} is independently selected from the group consisting of a straight or branched alkylene and a straight or branched alkenylene chain.

Of this class of compounds, one preferred subclass of compounds is that subclass wherein:

R^1 is $-OR^7$;

R^2 is $-R^8-OR^7$;

R^3 is $-R^8-OR^7$;

R^{4a} and R^{4b} are each independently selected from hydrogen, alkyl, alkenyl or alkynyl;

or R^{4a} is hydrogen, alkyl, alkenyl or alkynyl and R^{4b} is a direct bond to the carbon at C16;

or R^{4a} and R^{4b} together form alkylidene or haloalkylidene;

R^5 is alkyl;

R^6 is hydrogen;

each R^7 is independently selected from the group consisting of hydrogen, alkyl, substituted aryl or optionally substituted aralkyl; and

each R^8 is independently selected from the group consisting of a direct bond, a straight or branched alkylene chain, and a straight or branched alkenylene chain.

Of this class of compounds, another preferred subclass of compounds is that subclass wherein:

R^1 is $-OR^7$;

R^2 is $-R^8-OR^7$;

R^3 is $-R^{10}-N(R^7)_2$;

R^{4a} and R^{4b} are each independently selected from hydrogen, alkyl, alkenyl or alkynyl;

or R^{4a} is hydrogen, alkyl, alkenyl or alkynyl and R^{4b} is a direct bond to the carbon at C16;

or R^{4a} and R^{4b} together form alkylidene or haloalkylidene;

R^5 is alkyl or R^5 is a direct bond to the carbon at C14;

R^6 is hydrogen, $-R^8-OR^7$ or $-R^8-N(R^7)_2$;

each R^7 is independently selected from the group consisting of hydrogen, $-R^{10}-OR^9$, $-R^{10}-N(R^9)_2$, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

each R^8 is independently selected from the group consisting of a direct bond, a straight or branched alkylene chain, and a straight or branched alkenylene chain; and

each R^9 is independently selected from the group consisting of hydrogen, alkyl, aryl and aralkyl;

each R^{10} is independently selected from the group consisting of a straight or branched alkylene and a straight or branched alkenylene chain.

Of the preferred subgroup described above, another preferred class of compounds is that class wherein:

R^1 is $-OR^7$;

R^2 is $-R^{10}-N(R^7)_2$;

R^3 is selected from the group consisting of $-R^8-OR^7$, $-R^8-OC(O)R^9$, $-R^{10}-N(R^7)_2$, $-R^{10}-N(R^9)C(O)R^9$, $-R^{10}-N(R^9)S(O)_tR^9$ (where t is 1 or 2), $-R^{10}-N(R^9)C(NR^9)N(R^9)_2$, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, and optionally substituted heteroarylalkenyl;

R^{4a} and R^{4b} are each independently selected from hydrogen, alkyl, alkenyl

or alkynyl;

or R^{4a} is hydrogen, alkyl, alkenyl or alkynyl and R^{4b} is a direct bond to the carbon at C16;

or R^{4a} and R^{4b} together form alkylidene or haloalkylidene;

R^5 is alkyl or R^5 is a direct bond to the carbon at C14;

R^6 is hydrogen, $-R^8-OR^7$ or $-R^8-N(R^7)_2$;

each R^7 is independently selected from the group consisting of hydrogen, $-R^{10}-OR^9$, $-R^{10}-N(R^9)_2$, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

each R^8 is independently selected from the group consisting of a direct bond, a straight or branched alkylene chain, and a straight or branched alkenylene chain; and

each R^9 is independently selected from the group consisting of hydrogen, alkyl, aryl and aralkyl;

each R^{10} is independently selected from the group consisting of a straight or branched alkylene and a straight or branched alkenylene chain.

Of this preferred class of compounds, one preferred subclass of compounds is that subclass wherein:

R^1 is $-OR^7$;

R^2 is $-R^{10}-N(R^7)_2$;

R^3 is $-R^8-OR^7$;

R^{4a} and R^{4b} are each independently selected from hydrogen, alkyl, alkenyl or alkynyl;

or R^{4a} is hydrogen, alkyl, alkenyl or alkynyl and R^{4b} is a direct bond to the carbon at C16;

or R^{4a} and R^{4b} together form alkylidene or haloalkylidene;

R^5 is alkyl or R^5 is a direct bond to the carbon at C14;

R^6 is hydrogen, $-R^8-OR^7$ or $-R^8-N(R^7)_2$;

each R^7 is independently selected from the group consisting of hydrogen, $-R^{10}-OR^9$, $-R^{10}-N(R^9)_2$, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

each R^8 is independently selected from the group consisting of a direct bond, a straight or branched alkylene chain, and a straight or branched alkenylene chain; and

each R^9 is independently selected from the group consisting of hydrogen, alkyl, aryl and aralkyl;

each R^{10} is independently selected from the group consisting of a straight or branched alkylene and a straight or branched alkenylene chain.

Of this preferred class of compounds, another preferred subclass of compounds is that subclass wherein:

R^1 is $-OR^7$;

R^2 is $-R^{10}-N(R^7)_2$;

R^3 is $-R^{10}-N(R^7)_2$;

R^{4a} and R^{4b} are each independently selected from hydrogen, alkyl, alkenyl or alkynyl;

or R^{4a} is hydrogen, alkyl, alkenyl or alkynyl and R^{4b} is a direct bond to the carbon at C16;

or R^{4a} and R^{4b} together form alkylidene or haloalkylidene;

R^5 is alkyl or R^5 is a direct bond to the carbon at C14;

R^6 is hydrogen, $-R^8-OR^7$ or $-R^8-N(R^7)_2$;

each R^7 is independently selected from the group consisting of hydrogen, $-R^{10}-OR^9$, $-R^{10}-N(R^9)_2$, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

each R^8 is independently selected from the group consisting of a direct

bond, a straight or branched alkylene chain, and a straight or branched alkenylene chain; and

each R^9 is independently selected from the group consisting of hydrogen, alkyl, aryl and aralkyl;

each R^{10} is independently selected from the group consisting of a straight or branched alkylene and a straight or branched alkenylene chain.

Of the group of compound first described above, another preferred subgroup of compounds is that subgroup wherein:

R^1 is $-N(R^7)_2$;

R^2 and R^3 are each independently selected from the group consisting of $-R^8-OR^7$, $-R^8-OC(O)R^9$, $-R^{10}-N(R^7)_2$, $-R^{10}-N(R^9)C(O)R^9$, $-R^{10}-N(R^9)S(O)_tR^9$ (where t is 1 or 2), $-R^{10}-N(R^9)C(NR^9)N(R^9)_2$, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, and optionally substituted heteroarylalkenyl;

R^{4a} and R^{4b} are each independently selected from hydrogen, alkyl, alkenyl or alkynyl;

or R^{4a} is hydrogen, alkyl, alkenyl or alkynyl and R^{4b} is a direct bond to the carbon at C16;

or R^{4a} and R^{4b} together form alkylidene or haloalkylidene;

R^5 is alkyl or R^5 is a direct bond to the carbon at C14;

R^6 is hydrogen, $-R^8-OR^7$ or $-R^8-N(R^7)_2$;

each R^7 is independently selected from the group consisting of hydrogen, $-R^{10}-OR^9$, $-R^{10}-N(R^9)_2$, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

each R^8 is independently selected from the group consisting of a direct bond, a straight or branched alkylene chain, and a straight or branched alkenylene chain; and

each R^9 is independently selected from the group consisting of hydrogen, alkyl, aryl and aralkyl;

each R^{10} is independently selected from the group consisting of a straight or branched alkylene and a straight or branched alkenylene chain.

Of the preferred class of compounds first described above, another preferred subclass of compounds is that subclass wherein:

R^1 is $-OR^7$;

R^2 is $-R^8-OR^7$;

R^3 is $-R^{10}-N(R^9)C(O)R^9$, $-R^{10}-N(R^9)S(O)_tR^9$ (where t is 1 or 2) or $-R^{10}-N(R^9)C(NR^9)N(R^9)_2$;

R^{4a} and R^{4b} are each independently selected from hydrogen, alkyl, alkenyl or alkynyl;

or R^{4a} is hydrogen, alkyl, alkenyl or alkynyl and R^{4b} is a direct bond to the carbon at C16;

or R^{4a} and R^{4b} together form alkylidene or haloalkylidene;

R^5 is alkyl or R^5 is a direct bond to the carbon at C14;

R^6 is hydrogen, $-R^8-OR^7$ or $-R^8-N(R^7)_2$;

each R^7 is independently selected from the group consisting of hydrogen, $-R^{10}-OR^9$, $-R^{10}-N(R^9)_2$, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

each R^8 is independently selected from the group consisting of a direct bond, a straight or branched alkylene chain, and a straight or branched alkenylene chain; and

each R^9 is independently selected from the group consisting of hydrogen, alkyl, aryl and aralkyl;

each R^{10} is independently selected from the group consisting of a straight or branched alkylene and a straight or branched alkenylene chain.

Of the preferred subgroup of compounds first described above, another

preferred class of compounds is that class wherein:

R^1 is $-OR^7$;

R^2 is selected from the group consisting of $-R^8-OC(O)R^9$, $-R^{10}-N(R^9)C(O)R^9$, $-R^{10}-N(R^9)S(O)_tR^9$ (where t is 1 or 2), $-R^{10}-N(R^9)C(NR^9)N(R^9)_2$, alkyl, alkenyl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted heterocyclylalkyl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl, and optionally substituted heteroarylalkenyl;

R^3 is $-R^8-OR^7$ or $-R^8-OC(O)R^9$;

R^{4a} and R^{4b} are each independently selected from hydrogen, alkyl, alkenyl or alkynyl;

or R^{4a} is hydrogen, alkyl, alkenyl or alkynyl and R^{4b} is a direct bond to the carbon at C16;

or R^{4a} and R^{4b} together form alkylidene or haloalkylidene;

R^5 is alkyl or R^5 is a direct bond to the carbon at C14;

R^6 is hydrogen, $-R^8-OR^7$ or $-R^8-N(R^7)_2$;

each R^7 is independently selected from the group consisting of hydrogen, $-R^{10}-OR^9$, $-R^{10}-N(R^9)_2$, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

each R^8 is independently selected from the group consisting of a direct bond, a straight or branched alkylene chain, and a straight or branched alkenylene chain; and

each R^9 is independently selected from the group consisting of hydrogen, alkyl, aryl and aralkyl;

each R^{10} is independently selected from the group consisting of a straight or branched alkylene and a straight or branched alkenylene chain.

Of the preferred class of compounds first described above, another subclass of compounds is that subclass wherein:

R^1 is $-OR^7$;

R^2 is $-R^8-OR^7$;

R^3 is heterocyclylalkyl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkenyl or optionally substituted heteroarylalkenyl;

R^{4a} and R^{4b} are each independently selected from hydrogen, alkyl, alkenyl or alkynyl;

or R^{4a} is hydrogen, alkyl, alkenyl or alkynyl and R^{4b} is a direct bond to the carbon at C16;

or R^{4a} and R^{4b} together form alkylidene or haloalkylidene;

R^5 is alkyl or R^5 is a direct bond to the carbon at C14;

R^6 is hydrogen, $-R^8-OR^7$ or $-R^8-N(R^7)_2$;

each R^7 is independently selected from the group consisting of hydrogen, $-R^{10}-OR^9$, $-R^{10}-N(R^9)_2$, alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl and optionally substituted heteroarylalkyl;

each R^8 is independently selected from the group consisting of a direct bond, a straight or branched alkylene chain, and a straight or branched alkenylene chain; and

each R^9 is independently selected from the group consisting of hydrogen, alkyl, aryl and aralkyl;

each R^{10} is independently selected from the group consisting of a straight or branched alkylene and a straight or branched alkenylene chain.

Of the preferred groups of compounds set forth above, the most preferred compounds of the invention are those compounds which are disclosed below in the "Synthesis Examples". Of the preferred groups of compounds set forth above, the most preferred R^1, R^2, R^3, R^{4a}, R^{4b}, R^5, R^6, R^7, R^8, R^9 and R^{10} selections may be discerned from the compounds which are disclosed below in the "Synthesis Examples". For example, the most preferred selection for R^{4a} and R^{4b} is when they together form a methylene or an ethylidene group. For example, a preferred selection for R^1 is $-R^8-OR^7$ where R^8 is a direct bond and R^7 is hydrogen. For example, a preferred selection for R^5

is methyl. For example, a preferred selection for R^6 is hydrogen. Similar preferred embodiments are readily discernible by the following disclosure and the attached claims.

Of the methods of treating an inflammatory condition or disease in a mammal by administering a compound of the invention, as set forth above in the Summary of the Invention, a preferred method administers a compound of formula (Ia). In addition, a preferred method is one wherein the inflammatory condition or disease is selected from the following:

arthritis (including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, osteoarthritis, gout, and synovitis), inflammations of the brain (including multiple sclerosis, Alzheimer's, AIDS dementia, stroke, encephalitis, trauma, and Creutzfeld-Jakob disease), inflammatory bowel disease (including Crohn's disease and ulcerative colitis), irritable bowel syndrome, ischemia-reperfusion injury (including myocardial infarction), sarcoidosis, psoriasis, tissue/organ transplant, graft *vs* host disease, systemic lupus erythematosus, Type I juvenile diabetes, vasculitis, artherosclerosis, cardiomyopathy, autoimmune myocarditis, atopic dermatitis, asthma, allergy, allergic rhinitis, and chronic obstructive pulmonary disease (including emphysema and bronchitis).

E. Preparation of the Compounds of the Invention

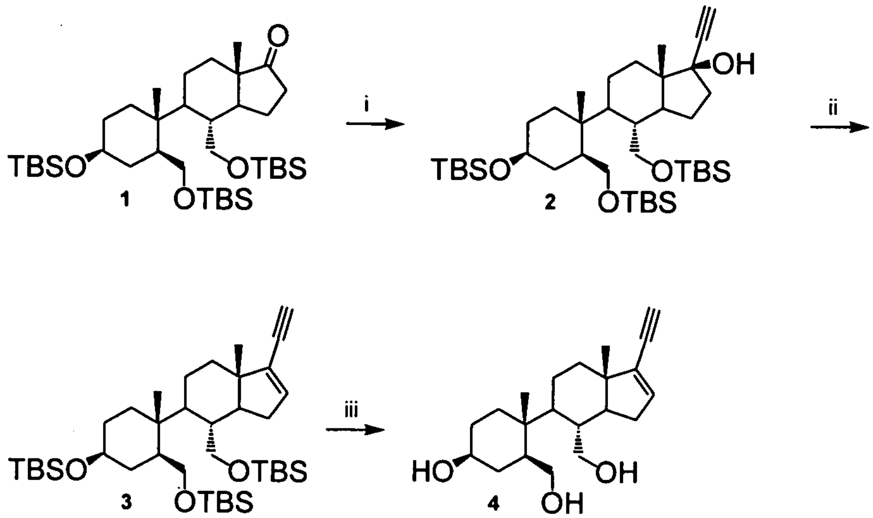
The compounds of the invention can be prepared by methods employing steps known to those skilled in the art or analogous to those steps. General methods for the reactions on steroids can be found in "Steroid Reactions", C. Djerassi, Ed. Holden Day, San Francisco, Calif., 1963 and references cited therein. General synthetic methods can be found in "Comprehensive Organic Transformations", R.C. Larock, VCH Publishers, New York, N.Y., 1989 and references cited therein. Additional literature references useful for the synthesis of compounds of the invention are as follows: T. Reichstein; C.H. Meystre, *Helv. Chim. Acta*, **1932**, *22*, 728; H. Westmijze; H. Kleyn; P. Vermeer; L.A. van Dijck, *Tet. Lett.* **1980**, *21*, 2665; K. Prezewowsky; R

Wiechert, US Pat. No. 3,682,983; P. Kaspar; H. Witzel, *J. Steroid Biochem.* **1985**, *23*, 259; W.G. Dauben; T. Brookhart, *J. Am. Chem. Soc.* **1981**, *103*, 237; A.J. Manson *et al.*, *J. Med. Chem.* **1963**, *6*, 1; R.O. Clinton *et al*, *J. Am. Chem. Soc.* **1961**, *83*, 1478; M.S. Ahmad; L.A. Khan, *Acta. Chim. Acad. Sci. Hung.* **1981**, *106*, 111.

In particular, compounds of the invention may be prepared by the following Schemes or by the Reaction Schemes disclosed in the following Synthesis Examples. It is understood that other compounds of the invention may be prepared in a similar manner as described below or by methods known to one of ordinary skill in the art. It is also understood that although the following Synthesis Examples may be directed to the preparation of a specific substituent on a particular carbon in the compounds, one of ordinary skill in the art would be able to prepare similar substituents on other carbons of the compounds based on the teachings provided herein and in view of what is commonly known in the art.

Referring to the following Scheme A, ketones of compound **1**, or compounds analogous thereto, can be alkylated with a variety of alkylating groups to give compounds of the invention having but not limited to alkyl, cycloalkyl, aryl and heteroaryl substitution. Alkylation of the 17-ketone **1** with the anion of acetylene generates the 17α-ethynyl-17β-hydroxyl intermediate **2**. Reversal of the stereochemistry of the C17 substituents may be carried out by first forming the methylsulfonate followed by treatment with silver (I) nitrate in tetrahydrofuran (THF) and water. Dehydration of compound **2** using $POCl_3$ in 2,4-lutidine gives compound **3**. Treatment with tetrabutylammonium fluoride removes the *tert*-butyldimethylsilyl groups to give compound **4**.

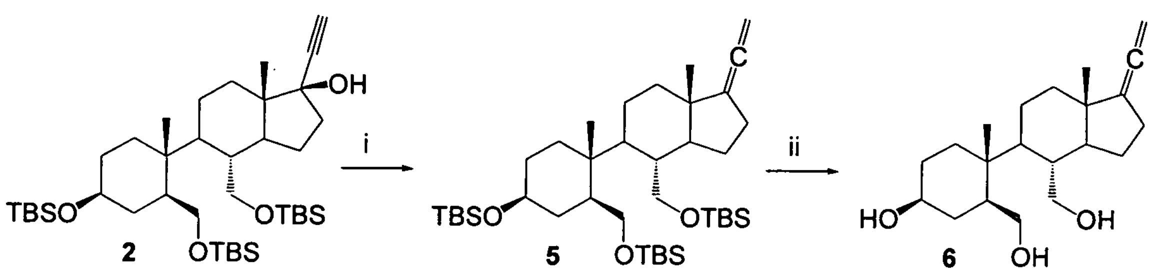
SCHEME A



i) KCCH; ii) $POCl_3$, 2,4-lutidine; iii) Bu_4NF.

Referring to the following Scheme B, compounds of the invention having an allene functionality may be prepared from intermediates analogous to compound **2**. Exemplary is the reaction of compound **2** with $LiAlH_4$ and $AlCl_3$ in THF to give the allene **5**. Treatment with tetrabutylammonium fluoride removes the *tert*-butyldimethylsilyl groups to give compound **6**.

SCHEME B

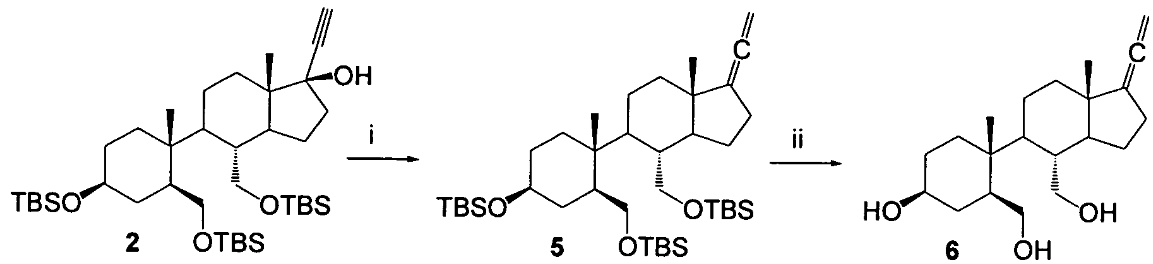


i) $LiAlH_4$, $AlCl_3$, THF; ii) Bu_4NF.

Referring to the following Scheme C, compounds of the invention having an alkynyl functionality may be prepared from allene intermediates. Exemplary is the treatment of compound **5** with n-BuLi in THF giving the 17β-ethynyl compound **7**.

Treatment with tetrabutylammonium fluoride removes the *tert*-butyldimethylsilyl groups to give compound **8**.

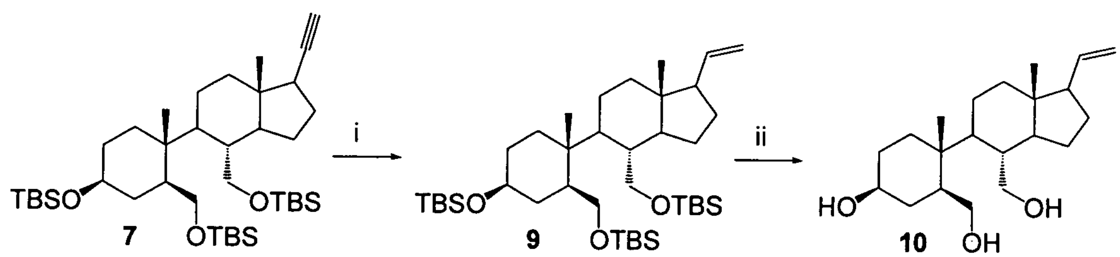
SCHEME C



i) n-BuLi, THF; ii) Bu_4NF.

Referring to the following Scheme D, compounds of the invention having alkenyl functionality may be prepared from alkyne intermediates. Exemplary is the controlled hydrogenation of compound **7** using Pd-$CaCO_3$ as catalyst to give the alkene **9**. Treatment with tetrabutylammonium fluoride removes the *tert*-butyldimethylsilyl groups to give compound **10**.

SCHEME D

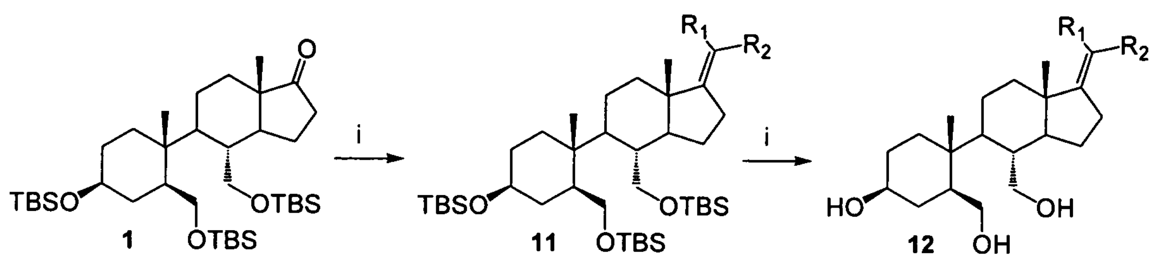


i) H_2, Pd-$CaCO_3$; ii) Bu_4NF.

Compound **1** can be used in a multitude of olefination reactions, including Wittig-type reactions to provide compounds of the invention having an exocyclic olefin. For example, as illustrated in the following Scheme E, compound **1** may be treated with ethyltriphenylphosphonium bromide and potassium *tert*-butoxide to provide compound **11** having R_1 = methyl and R_2 = hydrogen. Treatment with tetrabutylammonium fluoride removes the *tert*-butyldimethylsilyl groups to give compound **12**.

In analogy to the synthesis shown in the following Scheme E, ketones such as compound **1** may be reacted with other Wittig-type reagents such as, but not limited to, methyl-, propyl-, butyl-, pentyl- or hexyltriphenyl-phosphonium bromide to give compounds of the invention analogous to compound **12** having R_2 = hydrogen and R_1 = hydrogen, ethyl, propyl, butyl or pentyl.

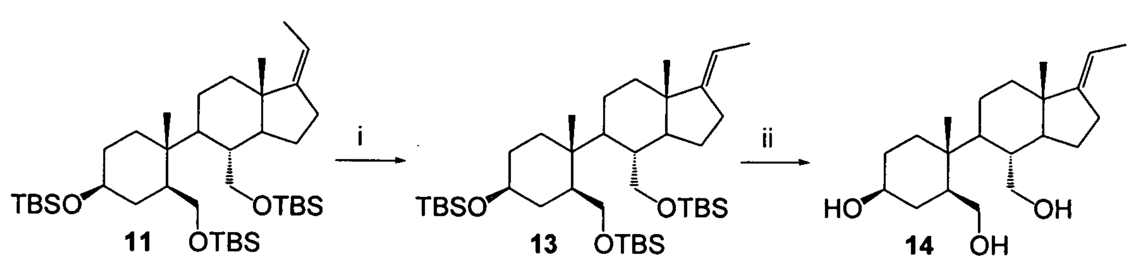
SCHEME E



i) $EtPPh_3Br$, KO^tBu, Toluene; ii) Bu_4NF.

Compounds of the invention can contain exocyclic double bonds of *E* and/or *Z* geometry. For example, as illustrated in the following Scheme F, the *Z*-olefin **11** in cyclohexane may be treated with UV light in the presence of diphenyl disulfide resulting in isomerization to the *E*-olefin **13**. Treatment with tetrabutylammonium fluoride removes the *tert*-butyldimethylsilyl groups to give compound **14**.

SCHEME F

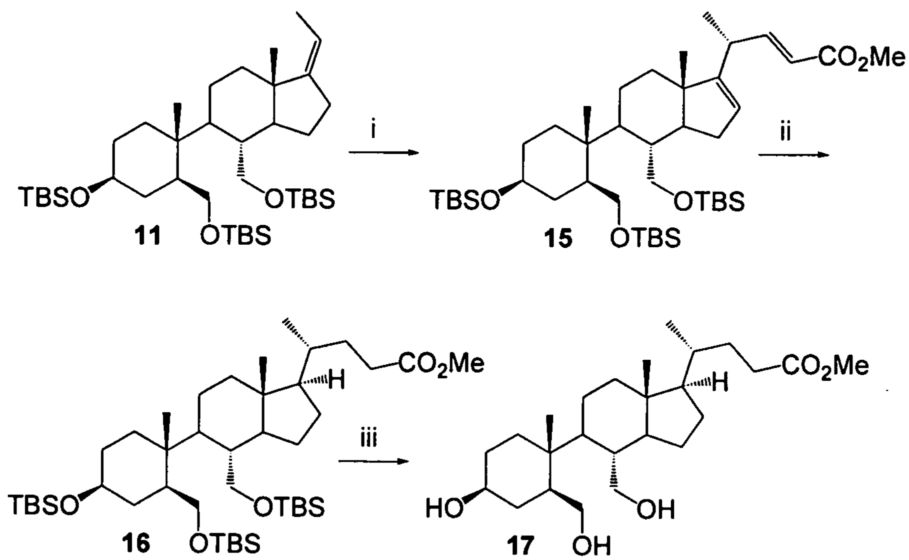


i) $(PhS)_2$, hυ, cyclohexane; ii) Bu_4NF.

A multitude of compounds of the invention having functionalized sidechains can be prepared using methods such as Lewis acid promoted couplings to aldehydes and Michael acceptors. For example, as illustrated in the following Scheme

G, compound **11** may be reacted with methyl propiolate in the presence of diethylaluminum chloride to give compound **15**. The double bonds may be hydrogenated using a catalyst such as platinum to give compound **16**. Treatment with tetrabutylammonium fluoride removes the *tert*-butyldimethylsilyl groups to give compound **17**.

SCHEME G



i) $HCCCO_2Me$, Et_2AlCl; ii) H_2, Pt; iii) Bu_4NF.

The following specific examples are provided as a guide to assist in the practice of the invention, and are not intended as a limitation on the scope of the invention.

Unless otherwise stated, flash chromatography and column chromatography used in the following examples may be accomplished using Merck silica gel 60 (230-400 mesh). Flash chromatography may be carried out according to the procedure set forth in: "Purification of Laboratory Chemicals", 3rd. edition, Butterworth-Heinemann Ltd., Oxford (1988), Eds. D. D. Perrin and W. L. F. Armarego, page 23. Column chromatography refers to the process whereby the flow rate of eluent through a packing material is determined by gravity. In all cases flash chromatography and radial chromatography may be used interchangeably. Radial chromatography may

be performed using silica gel on a Chromatotron Model # 7924T (Harrison Research, Palo Alto, California). Unless otherwise stated, quoted R_f values are obtained by thin layer chromatography using Silica Gel 60 F_{254} (Merck KGaA, 64271, Darmstadt, Germany). Brine refers to a saturated solution of sodium chloride.

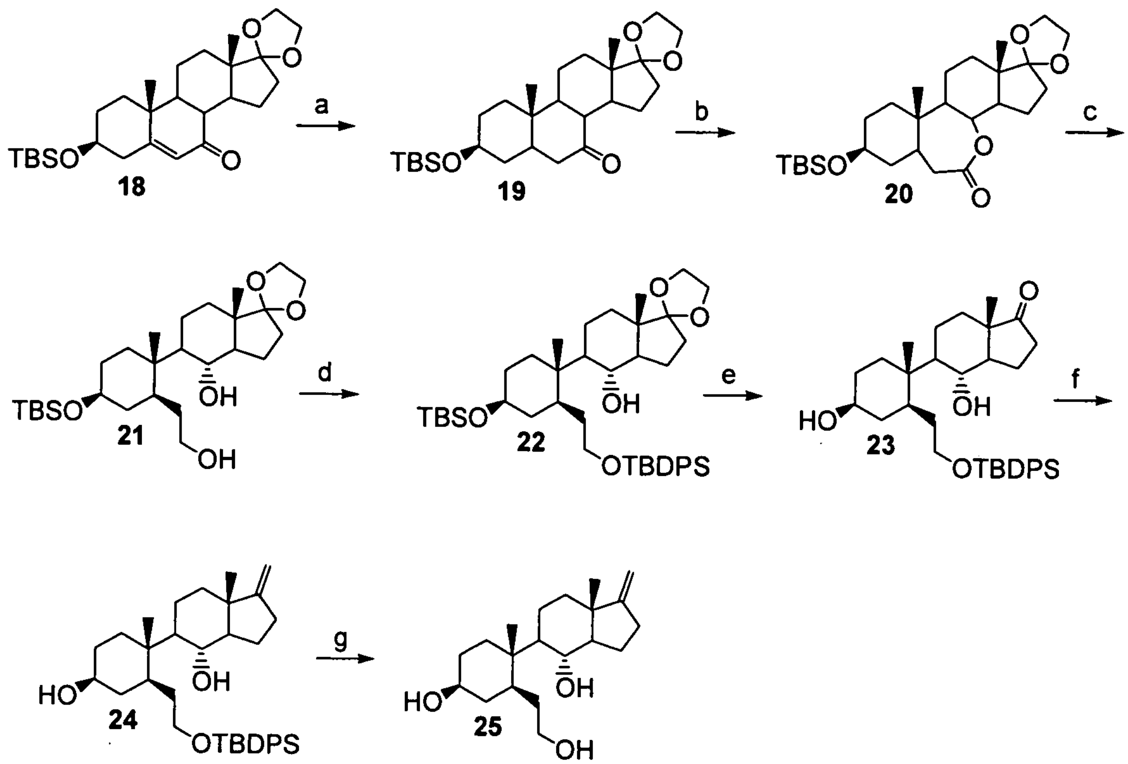
Also, unless otherwise stated, chemical reactants and reagents were obtained from standard chemical supply houses, such as Aldrich (Milwaukee, WI; www.aldrich.sial.com); EM Industries, Inc. (Hawthorne, NY); Fisher Scientific Co. (Hampton, NH); and Lancaster Synthesis, Inc. (Windham, NH). Gases were obtained from Praxair (Vancouver, B.C.). Cell lines, unless otherwise stated, where obtained from public or commercial sources, *e.g.*, American Tissue Culture Collection (ATCC, Rockville, MD).

SYNTHESIS EXAMPLES

EXAMPLE 1

Compound **25**, a representative compound of the invention, may be prepared according to Reaction Scheme 1. Any number of compounds related to compound **25** could be produced using similar methodology. Starting compound **18** may be prepared according to the procedures outlined in U.S. Patent 6,046,185.

REACTION SCHEME 1



a) H_2, Pd/C, EtOAc; b) MCPBA, $CHCl_3$; c) $LiAlH_4$, THF; d) TBDPSCl, imidazole, DMF; e) 80% AcOH; f) $MePPh_3Br$, KO^tBu, THF; g) BuN_4F, THF, reflux.

In general, hydrogenation of compound **18** using Pd on carbon as catalyst gives compound **19**. Baeyer-Villager oxidation using 3-chloroperoxybenzoic acid (MCPBA) in $CHCl_3$ gives the lactone compound **20**. Lithium aluminum hydride reduction of the lactone in THF gives the diol compound **21**. Reaction of compound **21** with *tert*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole in DMF protects the primary hydroxyl in compound **22**. Treatment with 80% acetic acid removes the ketal and the *tert*-butyldimethylsilyl (TBS) group to give compound **23**. Olefination of compound **23** using methyltriphenyl-phosphonium bromide and KO^tBu in THF gives the methylidene compound **24**. Treatment with a refluxing solution of Bu_4NF in THF removes the TBDPS group to give compound **25**.

Following are specific examples of the compounds prepared above.

Synthesis of compound **19**

A solution of compound **18** (2.03 g, 4.41 mmol) in EtOAc (135 mL) was treated overnight with hydrogen (balloon pressure) in the presence of a catalytic amount of Pd on carbon. The catalyst was removed by filtration and the solution was concentrated to dryness. The residue was purified by chromatography on silica gel (hexanes/EtOAc/CH_2Cl_2, 8:1:1) to give compound **19** (1.79 g, 88 %) as a white solid.

Synthesis of compound **20**

A mixture of compound **19** (2.38 g, 5.14 mmol) and MCPBA (3.11 g, 10.3 mmol) in chloroform (26 mL) was refluxed for 4 hours. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc (25 mL), washed with saturated Na_2SO_3 (2 x 20 mL), saturated $NaHCO_3$ (2 x 20 mL) and brine (2 x 20 mL) then dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude compound **20** (2.43 g, white solid) was used for the next reaction without further purification.

Synthesis of compound **21**

To a solution of compound **20** (1.00 g, 2.09 mmol) in THF at 0°C was added $LiAlH_4$ (21 mL of a 1 M solution in THF, 2.09 mmol). The reaction mixture was stirred at ambient temperature for one hour then brine (5 mL) was slowly added. The solution was extracted with CH_2Cl_2 (2 x 15 mL) then was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc) to afford compound **21** (0.786 g, 78 %) as a white solid.

Synthesis of compound **22**

A solution of compound **21** (0.93 g, 1.93 mmol), TBDPSCl (1.1 mL, 4.4 mmol) and imidazole (0.57 g, 8.5 mmol) in dry DMF (10 mL) was stirred overnight. The reaction mixture was diluted with EtOAc (50 mL) and washed with brine (2 x 20mL) then was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 3:1) to afford compound **22** (1.22 g, 66%) as a white solid.

Synthesis of compound **23**

A mixture of compound **22** (1.00 g, 1.39 mmol) and 80% acetic acid (20

mL)) was stirred at 50°C for 2 hours then was diluted with toluene (30 mL) and concentrated. The crude compound **23** was used for the next reaction without further purification.

Synthesis of compound **24**

A mixture of KO^tBu (0.487 g, 4.12 mmol) and $MePPh_3Br$ (1.47 g, 4.12 mmol) in THF (6 mL) was stirred at ambient temperature for 1 hour under argon then compound **23** (0.773 g, 1.37 mmol) in THF (6 mL) was added. The reaction mixture was stirred at ambient temperature overnight then was diluted with EtOAc (40 mL) and washed with brine (2 x 30 mL) then was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 1:1) to afford compound **24** (0.606 g, 79%) as a white solid.

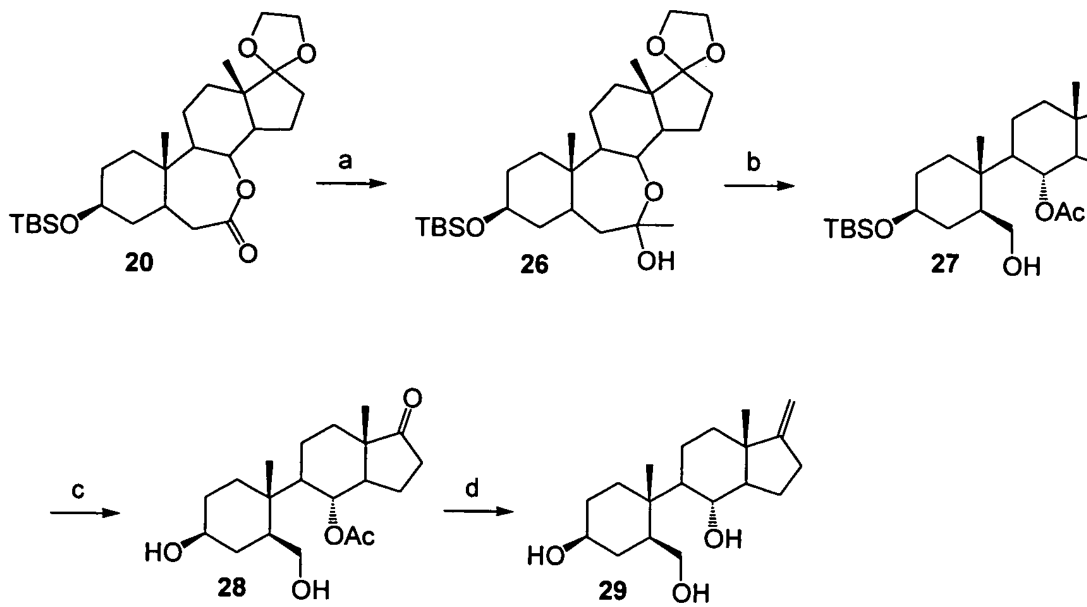
Synthesis of compound **25**

A solution of compound **24** (0.15 g, 0.267 mmol) and Bu_4NF (0.4 mL of a 1.0 M solution in THF) in THF (5 mL) was refluxed under argon for 2 hours. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (MeOH/EtOAc, 2:98) to give compound **25** (0.073g, 82%) as a white solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 287.10; $C_{20}H_{31}O$.

EXAMPLE 2

Compound **29**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 2. Any number of compounds related to compound **29** could be produced using similar methodology. Starting compound **20** may be prepared according to procedures set forth in Example 1 above.

REACTION SCHEME 2



a) MeLi, THF; b) MCPBA, $CHCl_3$; c) 80% AcOH; d) $MePPh_3Br$, KO^tBu, THF, reflux.

In general, treatment of lactone compound **20** with MeLi in THF gives the lactol compound **26**. Baeyer-Villager oxidation using MCPBA in $CHCl_3$ gives compound **27**. Treatment with 80% acetic acid removes the ketal and the TBS group to give compound **28**. Reaction of compound **28** with methyltriphenyl-phosphonium bromide and KO^tBu in THF introduces the methylidene group and removes the acyl group to give compound **29**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **26**</u>

To a 0°C solution of compound **20** (2.0 g, 4.18 mmol) in dry THF (12 mL) was added dropwise MeLi (8.95 mL of a 1.4 M solution in ether). The reaction mixture was stirred for 2 hours then was poured over ice and extracted with EtOAc (3 x 100 mL). The combined organic layer was washed with brine (2 x 50 mL) then was dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc, 8:2) to yield compound **26** (1.49 g, 72 %) as a white solid.

Synthesis of compound **27**

To a solution of compound **26** (1.49 g, 3.00 mmol) in chloroform was added MCPBA (1.8 g, 6.00 mmol). The reaction mixture was stirred at ambient temperature for 20 hours then was diluted with EtOAc (200 mL). The solution was washed successively with 5% $NaHSO_3$ solution (2 x 100 mL), saturated K_2CO_3 solution (2 x 50 mL) and brine (2 x 50 mL) then was dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc, 9:1) to afford compound **27** (1.3 g, 85 %) as a white solid.

Synthesis of compound **28**

A mixture of compound **27** (400 mg, 0.783 mmol) and 80% acetic acid (5 mL) was stirred at 50°C for 5 hours then was diluted with toluene (50 mL) and concentrated. The residue was purified by chromatography on silica gel (hexanes/acetone, 1:1) to yield compound **28** (322 mg, 86%) as a white solid.

Synthesis of compound **29**

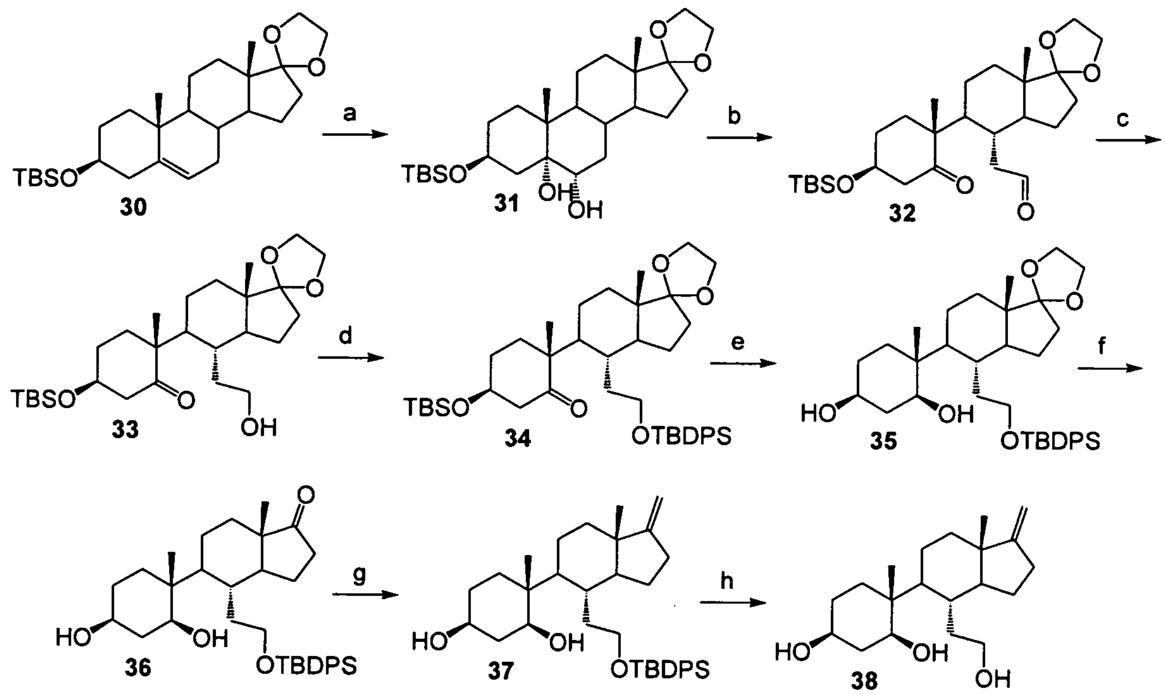
A mixture of KO^tBu (286 mg, 2.55 mmol) and $MePPh_3Br$ (911 mg, 2.55 mmol) in THF (2 mL) was stirred at ambient temperature for 1 hour under argon, then compound **28** (300 mg, 0.85 mmol) in THF (2 mL) was added. The reaction mixture was refluxed for 4 hours then was cooled to ambient temperature and diluted with water (5 mL). The solution was extracted with EtOAc (3 x 50 mL) and washed with brine (2 x 20 mL) then was dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 2:8) to afford compound **29** (144 mg, 55%) as a white solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 273.01; $C_{19}H_{29}O$.

EXAMPLE 3

Compound **38**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 3. Any number of compounds related to compound **38** could be produced using similar methodology. Starting compound **30** may be prepared according to the procedures outlined in U.S. Patent

6,046,185.

REACTION SCHEME 3



a) OsO_4, pyridine; b) $Pb(OAc)_4$, CH_2Cl_2; c) $LiEt_3BH$, THF; d) TBDPSCl, imidazole, DMF; e) $LiAlH_4$, THF; f) 80% HOAc; g) CH_3PPh_3Br, KO^tBu, THF; h) Bu_4NF, THF, reflux.

In general, dihydroxylation of compound **30** using osmium tetraoxide in pyridine gives compound **31**. Oxidative cleavage of the diol using lead tetraacetate in CH_2Cl_2 gives compound **32**. Selective reduction of the aldehyde group using $LiBEt_3H$ in THF gives compound **33**. Reaction of compound **33** with TBDPSCl and imidazole in DMF protected the free hydroxyl to give compound **34**. Lithium aluminum hydride reduction of the ketone group gives compound **35**. Treatment with 80% acetic acid removes the ketal to give compound **36**. Olefination using methyltriphenylphosphonium bromide and KO^tBu in THF gives the methylidene compound **37**. Treatment with a refluxing solution of Bu_4NF in THF removes the TBDPS group to give compound **38**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound 31</u>

To a solution of compound **30** (0.45 g, 0.89 mmol) in pyridine (2.5 mL)

was added OsO_4 (0.25 g, 0.98 mmol). The reaction mixture was stirred at 90°C overnight then a solution of $Na_2S_2O_3$ (0.5 g) in a mixture of water (8 mL) and pyridine was added. The reaction mixture was stirred for 20 minutes then extracted with CH_2Cl_2 (2 x 20 mL) and washed with brine (30 mL), then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 4:1) to afford compound **31** (0.249 g, 58%) as a white solid.

Synthesis of compound **32**

To a solution of compound **31** (0.52 g, 1.08 mmol) in CH_2Cl_2 was added $Pb(OAc)_4$ (0.527 g, 1.19 mmol). The reaction mixture was stirred at ambient temperature for 10 minutes under argon. A precipitate was removed by filtration and the solvent was evaporated under reduced pressure. The residue was filtered through a silica gel plug (hexanes/EtOAc, 1:1) to afford compound **32** (0.482 g, 58%) as a white solid.

Synthesis of compound **33**

To a solution of compound **32** (0.562 g, 1.17 mmol) in THF at 0°C was added $LiBEt_3H$ (1.29 mL of a 1M solution in THF). The reaction mixture was stirred at ambient temperature for 40 minutes under argon then was cooled in an ice bath and NaOH (1.29 mL, 1M) and H_2O_2 (0.2 mL, 30%) were slowly added. The resulting solution was stirred at 0°C for an additional 5 minutes. The solution was extracted with CH_2Cl_2 (2 x 15 mL) and the extracts were dried over $MgSO_4$, filtered concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 75:25 to 40:60) to afford compound **33** (256 mg, 46%) as a white solid.

Synthesis of compound **34**

A solution of compound **33** (0.185 g, 0.385 mmol), TBDPSCl (0.175 mL, 0.673 mmol) and imidazole (0.09 g, 1.161 mmol) in dry DMF (4 mL) was stirred overnight. The reaction mixture was diluted with toluene (30 mL) and washed with brine (2 x 15 mL) then was dried over $MgSO_4$, filtered and concentrated. The crude compound **34** was used for the next reaction without further purification.

Synthesis of compound **35**

To a solution of compound **34** (crude, 0.104 mmol) in THF at 0°C was added $LiAlH_4$ (0.1 mL of a 1M solution in THF) under argon. The reaction mixture was stirred at 0°C for 1 hour, then brine (5 mL) was slowly added. The solution was extracted with CH_2Cl_2 (2 x 15 mL) and the extracts were dried over $MgSO_4$, filtered concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 2:3) to afford compound **35** (39 mg, 51% over two steps) as a white solid.

Synthesis of compound **36**

A mixture of compound **35** (120 mg, 0.197mmol) and 80% acetic acid (1.5 mL) was stirred at ambient temperature overnight then was diluted with toluene (10 mL) and concentrated. The crude compound **36** was used for the next reaction without further purification.

Synthesis of compound **37**

A mixture of KO^tBu (60 mg, 0.54 mmol) and $MePPh_3Br$ (194 mg, 0.54 mmol) in THF (0.9 mL) was stirred at ambient temperature for 1 hour under argon then compound **36** (97 mg, 0.17 mmol) was added. The reaction mixture was stirred at ambient temperature for 3 hours then was diluted with EtOAc (80 mL) and washed with brine (2 x 30 mL) then was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 2:3) to afford compound **37** (63 mg, 65%) as a white solid.

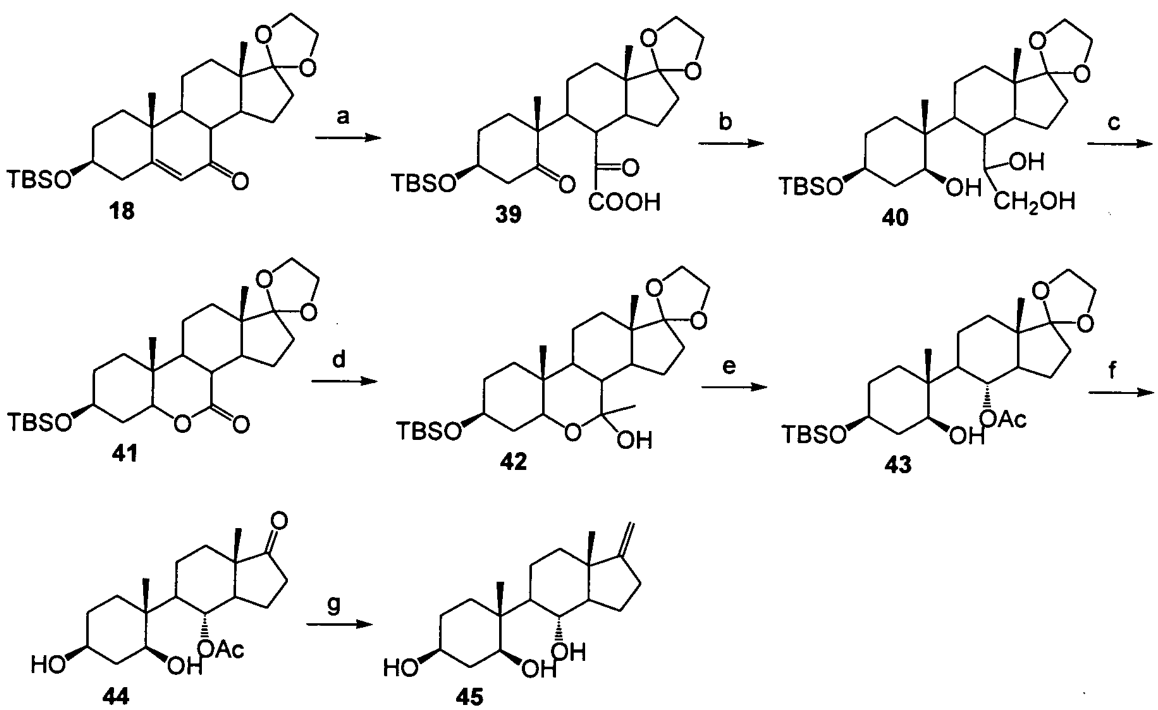
Synthesis of compound **38**

A solution of compound **37** (59 mg, 0.105 mmol) and n-Bu_4NF (0.16 mL of a 1.0 M solution in THF) in THF (0.35 mL) was refluxed under argon for 2 hours. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (MeOH/EtOAc, 2:98) to afford compound **38** (38 mg) as a white solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 286.93; $C_{20}H_{31}O$.

EXAMPLE 4

Compound **45**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 4. Any number of compounds related to compound **45** could be produced using similar methodology. Starting compound **18** may be prepared according to procedures outlined in U.S. Patent 6,046,185.

Reaction Scheme 4



a) $NaIO_4$, $RuO_2.H_2O$, CCl_4, acetone, H_2O; b) $LiAlH_4$, THF; c) $Pb(OAc)_4$, CH_2Cl_2; d) MeLi, THF; e) MCPBA, $CHCl_3$; f) 80% AcOH, 50°C; g) CH_3PPh_3Br, KO^tBu, THF; K_2CO_3, MeOH, reflux.

In general, oxidative ring opening of compound **18** using sodium periodate and a catalytic amount of ruthenium oxide gives compound **39**. Reaction with lithium aluminum hydride in THF gives compound **40**. Oxidative cleavage of the diol using lead tetraacetate in CH_2Cl_2 gives lactone compound **41**. Treatment with MeLi in THF gives the lactol compound **42**. Baeyer-Villager oxidation using MCPBA in $CHCl_3$ gives compound **43**. Treatment with 80% acetic acid removes the ketal and TBS group to give compound **44**. Reaction of compound **44** with methyltriphenylphosphonium

bromide and KO^tBu in THF introduces the methylidene group and subsequent treatment with K_2CO_3 in refluxing methanol removes the acyl group to give compound **45**.

Following are specific examples of the compounds prepared above.

Synthesis of compound **39**

To a solution of $NaIO_4$ (13.96 g, 65.2 mmol) and $RuO_2{\cdot}H_2O$ (87 mg, 0.66 mmol) in water (120 mL) were added CCl_4 (80 mL) and acetone (100 mL). Compound **18** (crude, 0.81 mmol), in a mixture of CCl_4 (40 mL) and acetone (60 mL) was then slowly added. The reaction mixture was stirred at ambient temperature for 3 hours. The solution was extracted with CH_2Cl_2 (2 x 200 mL) and the combined organic layer was washed with brine (200 mL) then was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc/MeOH, 70:25:5) to afford compound **39** (3.41 g, 37%) as a white solid.

Synthesis of compound **40**

To a solution of compound **39** (0.509 g, 1.00 mmol) in THF was slowly added $LiAlH_4$ (3 mL of a 1 M solution in THF). The reaction mixture was stirred for 2 hours then saturated $NaHCO_3$ (5 mL) was slowly added. The solution was extracted with CH_2Cl_2 (2 x 20 mL) and the extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (MeOH/EtOAc, 5:95) to afford compound **40** (0.16 g, 32%) as a white glassy solid.

Synthesis of compound **41**

To a solution of compound **40** (0.16 g, 0.32 mmol) in CH_2Cl_2 was added $Pb(OAc)_4$ (0.156 g, 0.35 mmol). The reaction mixture was stirred at ambient temperature for 10 minutes under argon. A precipitate was removed by filtration and solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 9:1) to afford compound **41** (0.113 g, 87 %) as a white glassy solid.

Synthesis of compound **42**

To a solution of compound **41** (0.20 g, 0.43 mmol) in THF (3 mL) at 0°C was added MeLi (1.5 mL of a 1.4 M solution in diethyl ether) under argon. The reaction

mixture was stirred at ambient temperature for 2 hours then was quenched with saturated NH_4Cl (15 mL) and extracted with EtOAc (2 x 15 mL) then was dried over $MgSO_4$, filtered and concentrated. The crude compound **42** was used for the next reaction without further purification.

Synthesis of compound **43**

A mixture of compound **42** (crude, 0.43 mmol) and MCPBA (0.26 g, 57-86%, 1.51 mmol) in chloroform (3 mL) was stirred at ambient temperature for 1 day. The reaction mixture was diluted with EtOAc (15 mL) and washed successively with saturated Na_2SO_3 (20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL), then was dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 4:1) to afford compound **43** (66 mg, 31 % over two steps) as a white solid.

Synthesis of compound **44**

A mixture of compound **43** (0.40 g, 0.81 mmol) and 80% acetic acid (5 mL) was stirred at 50°C for 2 hours, then was diluted with toluene (20 mL) and concentrated. The crude compound **44** was used for the next reaction without further purification.

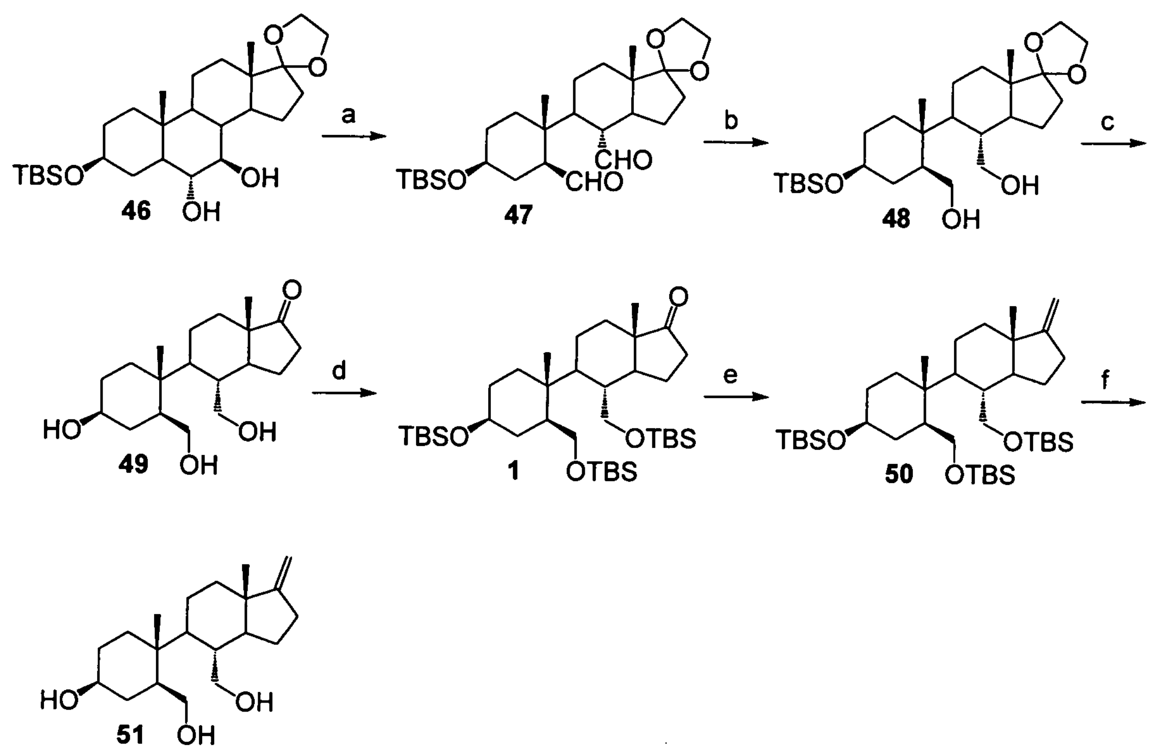
Synthesis of compound **45**

A mixture of KO^tBu (0.45 g, 4.05 mmol) and $MePPh_3Br$ (1.45 g, 4.05 mmol) in THF (10 mL) was stirred at ambient temperature for 1 hour under argon then compound **44** (crude, 0.81 mmol) in THF (5 mL) was added. The reaction mixture was stirred at ambient temperature overnight then was diluted with CH_2Cl_2 (50 mL) and washed with brine (2 x 30 mL), then dried over $MgSO_4$, filtered and concentrated. The crude product was refluxed with K_2CO_3 (0.34 g, 2.42 mmol) in THF (5 mL) for 3 hours. The solvent was removed and the residue was purified by chromatography on silica gel (hexane/EtOAc/MeOH, 5:5:0.5) to afford compound **45** (0.13 g, 55% over two steps) as a white solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 317.00; $C_{18}H_{30}NaO_3$.

EXAMPLE 5

Compound **51**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 5. Starting compound **46** may be prepared according to the procedures outlined in U.S. Patent 6,046,185. Any number of compounds related to compound **51** could be produced using similar methodology.

REACTION SCHEME 5



a) $NaIO_4$, THF; b) $NaBH_4$, MeOH, CH_2Cl_2; c) 80% AcOH; d) TBSCl, imidazole, DMF; e) CH_3PPh_3Br, KO^tBu, THF; f) 80% AcOH; Bu_4NF, THF.

In general, reaction of compound **46** with sodium periodate in THF oxidatively cleaves the diol to give compound **47**. Sodium borohydride reduction of the aldehyde groups gives compound **48**. Treatment with 80% acetic acid removes the ketal and TBS group to give compound **49**. Reaction with TBSCl and imidazole in DMF protected the hydroxyls to give compound **1**. Olefination using methyltriphenylphosphonium bromide and KO^tBu in THF gives compound **50**. Treatment with 80% acetic acid followed by a refluxing solution of Bu_4NF in THF

removes the TBS groups to give compound **51**.

Following are specific examples of the compounds prepared above.

Synthesis of compound **47**

A solution of compound **46** (450 mg, 0.94 mmol), $NaIO_4$ (240 mg, 1.12 mmol), water (2 mL) and THF (4 mL) was stirred overnight at ambient temperature. The reaction mixture was diluted with EtOAc and washed with brine then was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexanes, 15:85) to afford compound **47** (140 mg, 31%) as a white solid.

Synthesis of compound **48**

A solution of compound **47** (1.32 g, 2.76 mmol), $NaBH_4$ (229 mg, 6.06 mmol), MeOH (17 mL) and CH_2Cl_2 (3 mL) was stirred at 0°C for 4 hours, then at ambient temperature overnight. The solvents were evaporated under reduced pressure and the residue was diluted with EtOAc and washed with brine. The EtOAc layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexanes, 2:3) to afford compound **48** (0.35 g, 26%) as a white solid.

Synthesis of compound **49**

A mixture of compound **48** (350 mg, 0.72 mmol) and 80% acetic acid (20 mL) was stirred overnight at ambient temperature. The solvents were evaporated under reduced pressure and the residual solvent was removed by co-distillation with toluene to afford compound **49** (250 mg, 100%) as a yellow solid.

Synthesis of compound **1**

A solution of compound **49** (impure, 0.72 mmol), TBSCl (382 mg, 2.54 mmol), imidazole (346 mg, 5.08 mmol) in dry DMF (15 mL) was stirred at ambient temperature overnight. The reaction mixture was diluted with EtOAc (100 mL), washed with water, then was dried over Na_2SO_4, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexanes, 5:95) to afford compound **1** (374 mg, 78%).

Synthesis of compound **50**

A mixture of KO^tBu (191 mg, 1.7 mmol) and $MePPh_3Br$ (600 mg, 1.7 mmol) in THF (1.5 mL) was stirred at ambient temperature for 1 hour under argon, then compound **1** (374 mg, 0.56 mmol) in THF (1.5 mL) was added. The reaction mixture was heated at reflux for 3 hours then was diluted with water (3 mL) and extracted with EtOAc (30 mL). The EtOAc layer was washed with water (10 mL) and brine (10 mL) then was dried over Na_2SO_4, filtered and concentrated. The residue was eluted through silica gel (EtOAc/hexanes, 1:99) to afford compound **50** (354 mg, 95%) as a yellow oil.

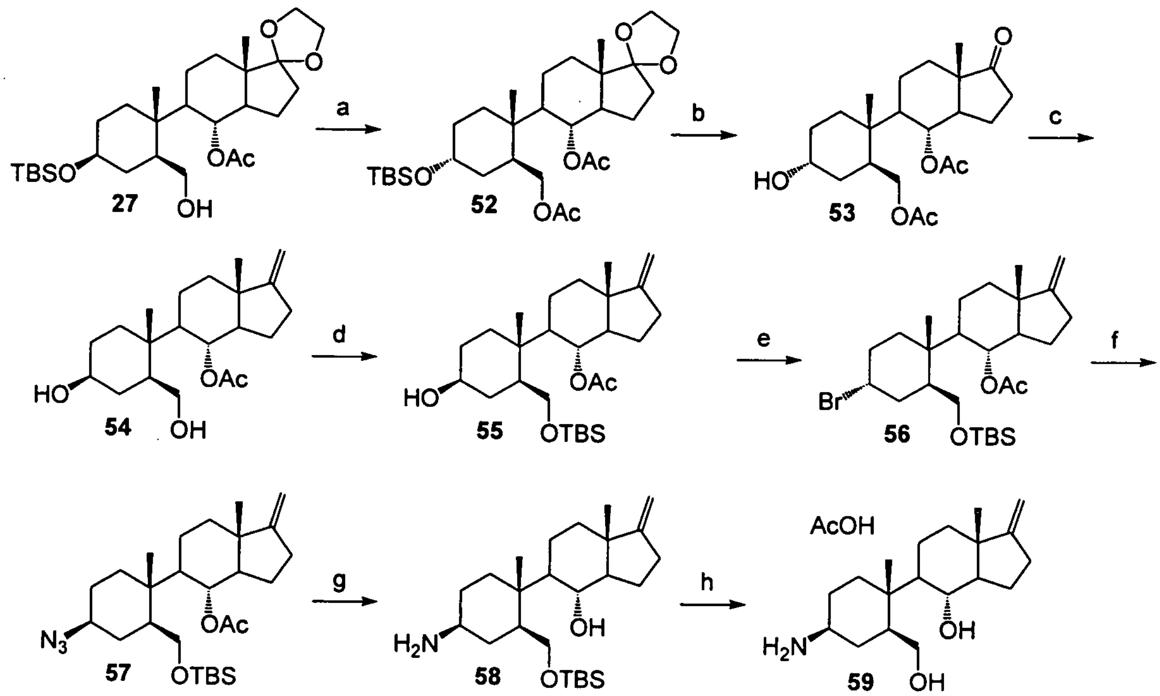
Synthesis of compound **51**

A mixture of compound **50** (350 mg, 0.53 mmol) and 80% acetic acid (10 mL) was heated at 50°C for 6 hours. The solvents were evaporated under reduced pressure and residual solvent was removed by co-distillation with toluene. The residue still contained some TBS protected material, therefore the residue was taken up in THF (1 mL) and Bu_4NF (2.5 mL of a 1.0 M solution in THF) and the resulting solution was heated at reflux for 3.5 hours. The reaction mixture was diluted with EtOAc and washed with water and brine then was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc) to afford compound **51** (119 mg, 70%) as a pale yellow solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 305.16; $C_{20}H_{32}O_2$, 287.19; $C_{20}H_{30}O$.

EXAMPLE 6

Compound **59**, a representative compound of the invention may be prepared according to the following Reaction Scheme 6. Any number of compounds related to compound **59** could be produced using similar methodology. Starting compound **27** may be prepared according to procedures described above in Example 2.

REACTION SCHEME 6



a) Ac_2O, DMAP, pyridine; b) 80% AcOH; c) CH_3PPh_3Br, KO^tBu, toluene; d) TBSCl, DMAP, Et_3N, DMF; e) Br_2, Ph_3P, Et_3N, THF; f) NaN_3, NMP; g) $LiAlH_4$, THF h) 80% AcOH, 50°C

In general, reaction of compound **27** with acetic anhydride and DMAP in pyridine gives compound **52**. Treatment with 80% acetic acid removes the ketal and the TBS group to give compound **53**. Reaction with methyltriphenylphosphonium bromide and KO^tBu in toluene introduces the methylidene group and removes the acyl group from the primary hydroxyl to give compound **54**. Treatment with TBSCl, DMAP and Et_3N in DMF selectively protects the primary hydroxyl to give compound **55**. The free hydroxyl in compound **55** is converted to the bromide compound **56** using bromine, triphenylphosphine and Et_3N in THF. Azide displacement of the bromine using sodium azide in NMP gives compound **57**. Reaction with lithium aluminum hydride in THF reduces the azide and removes the acyl group to give compound **58**. Treatment with 80% acetic acid removes the TBS group and forms the ammonium acetate salt to give compound **59**.

Following are specific examples of the compounds prepared above.

Synthesis of compound **52**

A solution of compound **27** (3.08 g, 5.87 mmol), acetic anhydride (1.12 mL, 11.7 mmol) and DMAP (50 mg, 0.41 mmol) in pyridine (25 mL) was stirred overnight. The reaction mixture was then quenched with brine (80 mL) and extracted with EtOAc (200 mL). The EtOAc layer was washed with brine (2 x 60 mL), then dried ($MgSO_4$), filtered and concentrated. The crude compound **52** was used directly in the next step.

Synthesis of compound **53**

A mixture of compound **52** (crude, 5.87 mmol) and 80% acetic acid (40 mL) was stirred at 50°C for 1 hour, then co-distilled with toluene (3 x 50 mL) and concentrated. The crude compound **53** was used directly in the next step.

Synthesis of compound **54**

A mixture of KO^tBu (2.02 g, 18.0 mmol) and $MePPh_3Br$ (6.43 g, 18.0 mmol) in toluene (45 mL) was stirred at ambient temperature for 1 hour under argon, then compound **53** (crude, 5.87 mmol) in toluene (10 mL) was added. The reaction mixture was stirred at ambient temperature overnight, then diluted with saturated NH_4Cl solution (100 mL) and extracted with EtOAc (100 mL). The EtOAc layer was washed with brine (80 mL), then dried ($MgSO_4$), filtered and concentrated. The residue was eluted through silica gel (hexanes/acetone, 7:3) to afford impure compound **54**.

Synthesis of compound **55**

A solution of compound **54** (impure, 2.85 mmol), TBSCl (490 mg, 3.25 mmol), DMAP (58 mg, 0.47 mmol) and Et_3N (600 μl, 4.3 mmol) in dry DMF (6 mL) was stirred for 5 hours. The reaction mixture was diluted with toluene (80 mL), washed with saturated $NaHCO_3$ solution and brine, then dried ($MgSO_4$), filtered and concentrated. The residue was purified by chromatography on silica gel to afford compound **55** (480 mg, 45%).

Synthesis of compound **56**

Bromine (80 μL, 1.6 mmol) was added to a solution of Ph_3P (407 mg, 1.6 mmol) in THF (5 mL) at ambient temperature. After 5 minutes Et_3N (290 μL, 2.1 mmol)

was added followed by a solution of compound **55** (480 mg, 1.03 mmol) in THF (5 mL). After 1.5 hours the reaction mixture was diluted with EtOAc (100 mL) and washed with water and brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (hexanes/EtOAc, 95:5) to afford compound **56** (510 mg, 94%).

Synthesis of compound **57**

A solution of compound **56** (510 mg, 0.97 mmol), NaN_3 (200 mg, 3.1 mmol) and NMP (8 mL) was heated at 55°C for 4 hours. The reaction mixture was diluted with toluene (100 mL) and EtOAc (30 mL) and washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (hexanes/EtOAc, 98:2) to afford compound **57** (197 mg, 41%).

Synthesis of compound **58**

To a solution of compound **57** (197 mg, 0.40 mmol) in THF at ambient temperature was added $LiAlH_4$ (1 mL of a 1.0 M solution in ether). The reaction mixture was stirred at ambient temperature for 2.5 hours then $Na_2SO_4 \cdot 10H_2O$ was added. The solution was filtered and the solid was washed with MeOH and CH_2Cl_2. The filtrate was concentrated and the residue was purified by chromatography on silica gel ($CHCl_3$/MeOH/Et_3N, 90:8:2) to afford compound **58** (144 mg, 78 %).

Synthesis of compound **59**

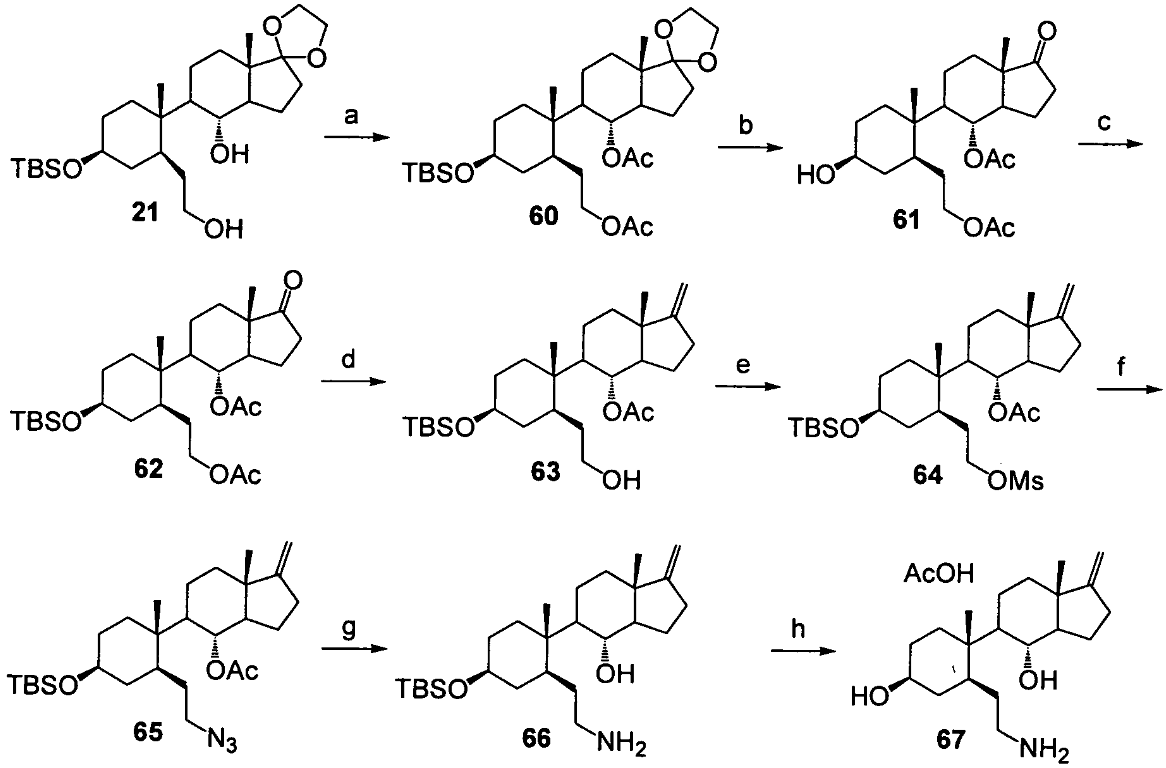
A mixture of compound **58** (114 mg, 0.27 mmol) and 80% acetic acid (7 mL) was stirred overnight at ambient temperature. The solution was diluted with toluene (3 x 50 mL) and concentrated to afford compound **59** (58 mg, 59%) as a yellow solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 307.92; $C_{19}H_{34}NO_2$.

EXAMPLE 7

Compounds **67** and **68**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 7. Any number of compounds related to compounds **67** and **68** could be produced using similar methodology. Starting

compound **21** may be prepared according to procedures described above in Example 1.

REACTION SCHEME 7



a) Ac_2O, pyridine; b) 80% AcOH, 50°C; c) TBSCl, imidazole, DMF; d) $MePPh_3Br$, KO^tBu, toluene; K_2CO_3, MeOH, reflux; e) MsCl, pyridine; f) NaN_3, DMF, 60°C; g) $LiAlH_4$, THF; h) 80% AcOH, 50°C.

In general, treatment of compound **21** with acetic anhydride in pyridine (to protects the free hydroxyls) gives compound **60**. Treatment with 80% acetic acid removes the ketal and the TBS groups to give compound **61**. Treatment with TBSCl and imidazole in DMF protects the free hydroxyl in compound **62**. Olefination of compound **62** with methyltriphenylphosphonium bromide and KO^tBu in toluene introduces the methylidene group. In some instances the olefination conditions result in removal of the acetate from the primary hydroxyl giving a compound such as **63**. The primary acetate may be selectively hydrolyzed by reaction with K_2CO_3 in refluxing methanol. The free hydroxyl in compound **63** is converted to the mesylate compound **64** using MsCl and pyridine. Azidation using sodium azide in DMF gives the azido compound **65**. Lithium aluminum hydride reduction of the azide in THF gives the amine

compound **66**. Treatment with 80% acetic acid removes the TBS group and forms the ammonium acetate salt to give compound **67**.

Following are specific examples of the compounds prepared above.

Synthesis of compound **60**

To a solution of compound **21** (0.686 g, 1.42 mmol) in pyridine (5 mL) was added acetic anhydride (0.94 mL, 9.94 mmol) and the reaction mixture was stirred at 50°C overnight. The solution was diluted with EtOAc (25 mL) and washed with brine (2 x 20 mL), then dried over $MgSO_4$, filtered and concentrated. The crude compound **60** was used for the next reaction without further purification.

Synthesis of compound **61**

A mixture of compound **60** (crude, 1.42 mmol) and 80% acetic acid (15 mL) was stirred at 50°C for 2 hours, then diluted with toluene (2 x 20 mL) and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 1:2) to afford compound **61** (0.479 g, 87%) as a white solid.

Synthesis of compound **62**

A solution of compound **61** (0.971 g, 2.38 mmol), TBSCl (0.716 g, 4.75 mmol) and imidazole (0.647 g, 9.51 mmol) in dry DMF (10 mL) was stirred for 3 hours. The reaction mixture was diluted with toluene (50 mL) and washed with brine (2 x 20 mL), then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 4:1) to afford compound **62** (1.218 g, 98%) as a viscous pale yellow oil.

Synthesis of compound **63**

A mixture of KO^{t}Bu (5.00 g, 42.3 mmol) and $MePPh_3Br$ (15.1 g, 42.3 mmol) in toluene (100 mL) was stirred at ambient temperature for 1 hour under argon, then a solution of compound **62** (crude, 14.1 mmol) in 100 mL of toluene was added. The reaction mixture was stirred overnight at ambient temperature, then quenched with saturated $NaHCO_3$ solution (75 mL) and water (75 mL). The solution was further diluted with 100 mL of water and was extracted with EtOAc (4 x 100 mL). The combined extracts solution was washed with brine (2 x 100 mL), then dried over

$MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 100:0, then 9:1, then 4:1) to afford the diacetate compound (4.5 g, 62%) as a yellow oil and compound **63** (1.8 g, 27%) as a yellow oil. A solution of the diacetate compound (4.5 g, 8.6 mmol), K_2CO_3 (4.78 g, 34.6 mmol) and methanol (100 mL) was heated at reflux under argon. After 75 minutes the reaction mixture was cooled to ambient temperature and filtered through celite eluting with CH_2Cl_2. The filtrate was concentrated and dissolved in EtOAc (250 mL), then washed with water and dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 100:0, then 19:1, then 9:1) to afford compound **63** (3.2 g, 47%) as a yellow foam.

<u>Synthesis of compound **64**</u>

To a solution of compound **63** (3.17 g, 6.62 mmol) in pyridine (50 mL) and CH_2Cl_2 (0.5 mL) was added methanesulfonyl chloride (1.02 mL, 13.2 mmol) and the reaction mixture was stirred under argon at ambient temperature for 3 hours. The reaction was quenched with saturated $NaHCO_3$ solution (60 mL) and extracted with EtOAc (3 x 80 mL). The combined extracts solution was washed with water and brine, then dried over $MgSO_4$, filtered and concentrated. The residue was concentrated from toluene to afford crude compound **64** that was used for the next reaction without further purification.

<u>Synthesis of compound **65**</u>

A solution of compound **64** (crude, 6.62 mmol) and NaN_3 (646 mg, 9.93 mmol) in DMF (40 mL) was heated under argon at 60°C overnight. After cooling, the reaction mixture was diluted with water (100 mL) and was extracted with diethyl ether (4 x 100 mL). The combined extracts solution was washed with water and brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 100:0, then 98:2, then 95:5) to afford compound **65** (2.56 g, 77% for 2 steps) as a yellow oil.

<u>Synthesis of compound **66**</u>

A solution of $LiAlH_4$ (3.85 mL of a 1.0 M solution in THF) was added to a

solution of compound **65** (647 mg, 1.28 mmol) in THF (15 mL) under argon. After 3 hours the reaction mixture was quenched with $Na_2SO_4 \cdot 10H_2O$ and diluted with THF (10 mL). After 30 minutes the solution was filtered and concentrated. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH/Et_3N, 100:0:0, then 95:5:0, then 90:10:0, then 95:5:2) to afford compound **66** (324 mg, 58%) as a colourless oil.

Synthesis of compound **67**

A solution of compound **66** (320 mg, 0.734 mmol) and 80% acetic acid (25 mL) was heated at 50°C for 3 hours. The residue was purified by chromatography on reverse-phase silica gel (H_2O, then H_2O/MeOH/AcOH 50:50:2). Concentration from MeOH/MeCN gave compound **67** (244 mg, 87%) as a white solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 322.12; $C_{20}H_{36}NO_2$.

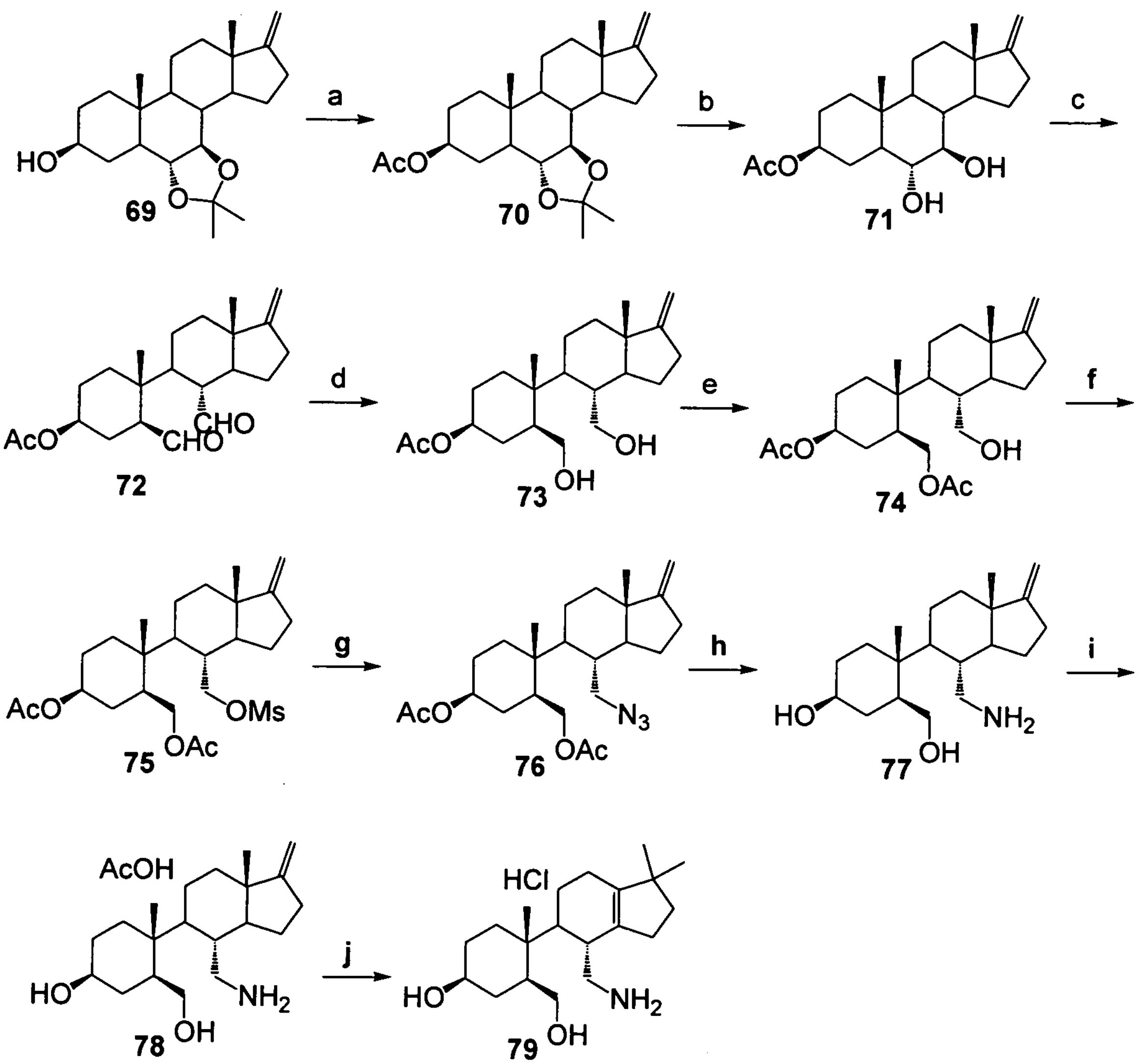
Synthesis of compound **68**

Using the procedures described for the synthesis of compound **67**, with the exception of olefination by $EtPPh_3Br$, compound **68** (75 mg) was prepared as a white solid in 22% yield starting from compound **62**. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 336.16; $C_{21}H_{38}NO_2$.

EXAMPLE 8

Compounds **77-81**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 8. Starting compounds such as **69** may be prepared according to the procedures outlined in U.S. Patent 6,046,185. Any number of compounds related to compounds **77-81** could be produced using similar methodology.

REACTION SCHEME 8



a) Ac_2O, DMAP, pyridine; b) 80% AcOH; c) $NaIO_4$, THF; d) $NaBH_4$, MeOH, THF; e) Ac_2O, DMAP, pyridine; f) MsCl, pyridine; g) NaN_3, DMF; h) $LiAlH_4$, THF; i) 80% AcOH; j) HCl, water, MeOH, 65°C.

In general, reaction of compound **69** with acetic anhydride and DMAP in pyridine gives compound **70**. Treatment with 80% acetic acid removes the acetonide group to give compound **71**. Reaction with sodium periodate in THF oxidatively cleaves the diol to give compound **72**. Sodium borohydride reduction of the aldehyde groups gives compound **73**. Reaction with acetic anhydride and DMAP in pyridine selectively protects the one primary hydroxyl to give compound **74**. The free hydroxyl is converted to the mesylate compound **75** using MsCl and pyridine. Reaction with sodium azide in

DMF gives the azido compound **76**. Reaction with lithium aluminum hydride in THF reduces the azide and removes the acyl groups to give compound **77**. Treatment with 80% acetic acid forms compound **78** as the ammonium acetate salt. Reaction of a compound such as **78** with HCl in water and MeOH facilitates migration of the 18-methyl group to C17 to give a compound such as **79**. Careful treatment of compound **77** with HCl in MeCN and water forms the ammonium chloride salt of compound **77** (*i.e.*, compound **80**).

Following are specific examples of the compounds prepared above.

Synthesis of compound **70**

A solution of compound **69** (6.9 g, 19.1 mmol), acetic anhydride (3.62 mL, 38.3 mmol) and DMAP (0.23 g, 1.9 mmol) in pyridine (50 mL) was stirred for 4.5 hours. The reaction mixture was diluted cold water (150 mL) and extracted with EtOAc (600 mL) and washed with brine (2 x 200 mL), then dried over $MgSO_4$, filtered and concentrated. The crude compound **70** was used directly in the next step.

Synthesis of compound **71**

A mixture of compound **70** (crude, 19.1 mmol) and 80% acetic acid (50 mL) was stirred at 40°C for 2 hours. The solution was concentrated to afford crude compound **71** that was used in the next step without further purification.

Synthesis of compound **72**

A solution of compound **71** (crude, 19.1 mmol), $NaIO_4$ (8.19 g, 38.3 mmol), water (53 mL) and THF (106 mL) was stirred at ambient temperature for 3.5 hours. The reaction mixture was diluted with CH_2Cl_2 and was washed with brine, then dried over $MgSO_4$, filtered and concentrated to afford crude compound **72** that was used in the next step without further purification.

Synthesis of compound **73**

A solution of compound **72** (crude, 19.1 mmol), $NaBH_4$ (1.45 g, 38.3 mmol), THF (120 mL) and MeOH (40 mL) was stirred at 0°C for 10 minutes, then at ambient temperature for 1 hour. The mixture was cooled in ice and 80% acetic acid (62 mL) was slowly added. The solution was stirred at ambient temperature for 10

minutes, then diluted with EtOAc (400 mL) and then washed with brine. The EtOAc layer was dried over $MgSO_4$, filtered and concentrated to afford crude compound **73** which was used in the next step without further purification.

Synthesis of compound **74**

A solution of compound **73** (crude, 19.1 mmol), acetic anhydride (2.1 mL, 22.0 mmol) and DMAP (230 mg, 1.9 mmol) in pyridine (65 mL) was stirred at ambient temperature for 1.5 hours. The reaction mixture was diluted with EtOAc (400 mL) and washed with brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 5:1 then 4:1 then 7:3) to afford compound **74** (4.9 g, 63%).

Synthesis of compound **75**

To a solution of compound **74** (4.9 g, 12.1 mmol) in pyridine (40 mL) was added methanesulfonyl chloride (1.68 mL, 21.7 mmol) and the reaction mixture was stirred at ambient temperature for 2 hours. The solution was diluted with EtOAc (400 mL) and washed with brine, then dried over $MgSO_4$, filtered and concentrated to afford crude compound **75** that was used for the next reaction without further purification.

Synthesis of compound **76**

A mixture of compound **75** (crude, 12.1 mmol) and NaN_3 (1.57 g, 24.1 mmol) in DMF (100 mL) was heated under argon at 60°C overnight. After cooling, the reaction mixture was diluted with toluene (400 mL) and was washed with brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 8:2) to afford compound **76** (4.8 g, 92% for 2 steps).

Synthesis of compound **77**

A solution of $LiAlH_4$ (44.5 mL of a 1.0 M solution in Et_2O) was added to an ice cooled solution of compound **76** (4.8 g, 11.1 mmol) in THF (111 mL). After 10 minutes the solution was continued at ambient temperature for another 4 hours. The reaction mixture was cooled in ice and quenched with $Na_2SO_4 \cdot 10H_2O$. After 15 minutes the solution was diluted with EtOAc (100 mL), stirred for an additional 20 minutes at

ambient temperature, then filtered. The filtrate was washed with brine, then dried over $MgSO_4$, filtered and concentrated to afford compound **77** (3.8 g, quantitative) as a white solid.

Synthesis of compound **78**

A solution of compound **77** (1.00 g, 2.93 mmol) and 80% acetic acid (15 mL) was heated at 40°C for 1 hour, then concentrated. Residual solvent was removed by codistillation with toluene. The residue was triturated in diethyl ether and filtered to give compound **78** (923 mg, 83%) as a white solid. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 321.95; $C_{20}H_{36}NO_2$.

Synthesis of compound **79**

A solution of compound **78** (600 mg, 1.57 mmol), concentrated HCl (5 drops), water (1 mL) and MeOH (9 mL) was heated at 65°C for 5 days, then concentrated. The residue was triturated in MeCN and filtered to give compound **79** (504 mg, 90%) as a white solid. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 322.2; $C_{20}H_{36}NO_2$.

Synthesis of compound **80**

To a suspension of compound **77** (0.1 g, 0.3 mmol) in MeCN (2 mL) was added HCl (337 μL of a 1.0 M solution in Et_2O). After 15 minutes the solution was filtered to afford the ammonium chloride salt of compound **77**, *i.e.*, compound **80** (76 mg, 72%) as a white powder.

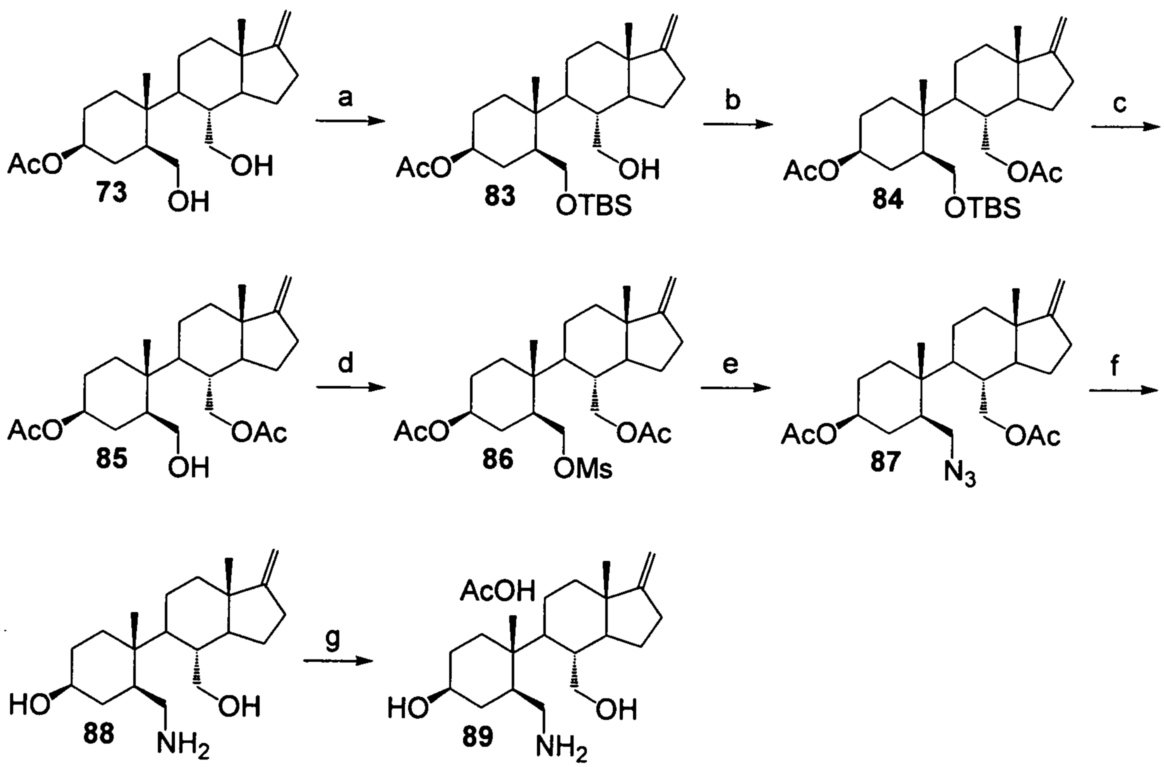
Synthesis of compound **81**

Using the procedures described for the synthesis of compound **80**, compound **81** (0.646 g) was prepared as a white powder in 37% yield starting from the ethylidene compound analogous to compound **69**. The salt formation step differed in that the compound was isolated by codistillation of the residual acid solution using MeOH: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 335.89; $C_{21}H_{38}NO_2$.

EXAMPLE 9

Compounds **88** and **89**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 9. Any number of compounds related to compounds **88-89** could be produced using similar methodology. Starting compound **73** may be prepared according to the procedures described above in Example 8.

REACTION SCHEME 9



a) TBSCl, imidazole, DMF; b) Ac_2O, DMAP, pyridine; c) Bu4NF, THF; d) MsCl, pyridine; e) NaN_3, DMF; f) $LiAlH_4$, THF; g) 80% AcOH.

In general, reaction of compound **73** with TBSCl and imidazole in DMF gives compound **83**. Reaction with acetic anhydride and DMAP in pyridine protects the remaining free hydroxyl to give compound **84**. Reaction with tetrabutylammonium fluoride removes the TBS group to give compound **85**. The free hydroxyl is converted to the mesylate compound **86** using MsCl and pyridine. Reaction with sodium azide in DMF gives the azido compound **87**. Reaction with lithium aluminum hydride in THF

reduces the azide and removes the acyl groups to give compound **88**. Treatment with 80% acetic acid forms the ammonium acetate salt to give compound **89**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **83**</u>

A solution of compound **73** (2.9 g, 7.92 mmol), TBSCl (1.32 g, 8.76 mmol), imidazole (813 mg, 11.9 mmol) and DMF (20 mL) was stirred at ambient temperature for 1.5 hours. The solution was diluted with water (50 mL) and was extracted with toluene (100 mL). The toluene layer was washed with brine (40 mL), then dried over $MgSO_4$, filtered and concentrated to give crude compound **83** that was used in the next step without further purification.

<u>Synthesis of compound **84**</u>

A solution of compound **83** (crude, 7.96 mmol), acetic anhydride (2.25 mL, 23.9 mmol) and DMAP (100 mg, 0.82 mmol) in pyridine (25 mL) was stirred at ambient temperature for 1 hour. The reaction mixture was diluted with EtOAc and washed with brine, then dried over $MgSO_4$, filtered and concentrated. The crude compound **84** was used in the next step without further purification.

<u>Synthesis of compound **85**</u>

A solution of compound **84** (crude g, 7.96 mmol), Bu_4NF (12 mL of a 1.0 M solution in THF) and THF was stirred at ambient temperature for 2 hours and at 40°C for 30 minutes. The reaction mixture was filtered through silica gel and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexanes 3:7) to afford compound **85** (2.06 g, 64%).

<u>Synthesis of compound **86**</u>

To a solution of compound **85** (1.06 g, 2.61 mmol) in pyridine (12 mL) was added methanesulfonyl chloride (400 μL, 5.16 mmol) and the reaction mixture was stirred at ambient temperature for 2 hours. The reaction was quenched with water and was extracted with EtOAc. The solution washed with brine, then dried over $MgSO_4$, filtered and concentrated to afford crude compound **86** which was used for the next reaction without further purification.

Synthesis of compound **87**

A mixture of compound **86** (crude, 2.61 mmol) and NaN_3 (1.0 g, 15 mmol) in DMF (15 mL) was heated under argon at 95°C overnight. After cooling, the reaction mixture was diluted with toluene and was washed with brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel to afford compound **87** (575 mg, 89%).

Synthesis of compound **88**

A solution of $LiAlH_4$ (3.2 mL of a 1.0 M solution in THF) was added to an ice cooled solution of compound **87** (274 mg, 0.635 mmol) in THF (3 mL). After 10 minutes the solution was continued at ambient temperature for another 3 hours. The reaction mixture was cooled in ice and quenched with $Na_2SO_4 \cdot 10H_2O$. After 15 minutes the solution was filtered and the filtrate was washed with brine, then dried over $MgSO_4$, filtered and concentrated. Purification by chromatography on silica gel ($EtOAc/MeOH/H_2O/NH_4OH$ 7:2:1:0.15, then 7:2:1:0.2, then 7:2:1:0.3) afforded compound **88** (135 mg, 66%).

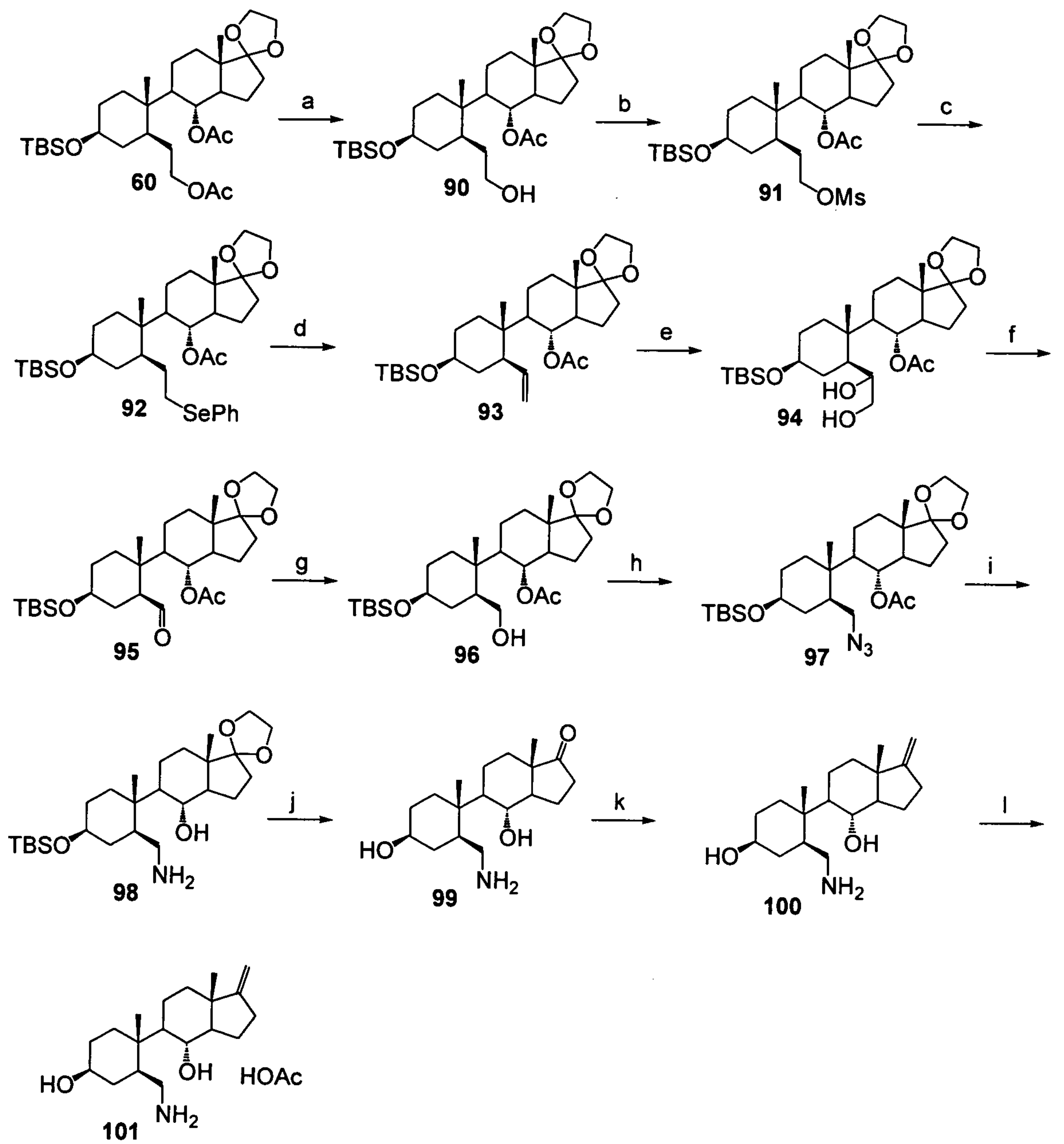
Synthesis of compound **89**

A solution of compound **88** (135 mg, 0.42 mmol) and 80% acetic acid (3 mL) was heated at 40°C for 30 minutes, then concentrated. Residual solvent was removed by codistillation with methanol to give compound **89** (158 mg, 99%) as a pale yellow foam. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 322.11; $C_{20}H_{36}NO_2$.

EXAMPLE 10

Compounds **100** and **101**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 10. Any number of compounds related to compounds **100** and **101** could be produced using similar methodology. Starting compound **60** may be prepared according to procedures described above in Example 7.

REACTION SCHEME 10



a) K_2CO_3, H_2O, MeOH, 55°C; b) MsCl, pyridine; c) $(SePh)_2$, $NaBH_4$, EtOH, 50°C; d) 30% H_2O_2, THF, 65°C; e) NMO, OsO_4, H_2O, ^tBuOH, THF; f) $Pb(OAc)_4$, CH_2Cl_2; g) $NaBH_4$, MeOH/THF; h) DIAD, DPPA, Ph_3P THF; i) LAH, THF; j) 2N HCl, THF; k) Ph_3PMeBr, KO^tBu, THF; l) HOAc

In general, selective hydrolysis of the primary acetate in compound **60** using K_2CO_3 gives compound **90**. The free hydroxyl is reacted to give the mesylate compound **91** using MsCl and pyridine. Mesylate displacement by phenylselenide gives

compound **92**. Oxidative elimination using hydrogen peroxide gives the olefin compound **93**. Osmolation gives dihydroxylated compound **94**, which is then oxidatively cleaved by lead tetraacetate to give compound **95**. Sodium borohydride reduction gives alcohol compound **96**. Azidation using diisopropyl azodicarboxylate (DIAD), diphenylphosphoryl azide (DPPA) and PPh_3 in THF gives the azido compound **97**. Reaction with lithium aluminum hydride in THF reduces the azide and removes the acyl group to give compound **98**. Treatment with HCl removes both the TBS group and the cyclic ketal to give compound **99**. Olefination using methyltriphenylphosphonium bromide and KO^tBu in THF gives compound **100**. Treatment with acetic acid forms the ammonium acetate salt to give compound **101**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **90**</u>

A mixture of compound **60** (12.7 g, 22.4 mmol), K_2CO_3, (9.38 g, 67.2 mmol), MeOH (250 mL) and water (94 mL) was stirred 55°C for 2 hours, cooled to ambient temperature then concentrated. The residue was dissolved in EtOAc, washed twice with saturated $NaHCO_3$ solution then twice with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc) to afford compound **90** (10.16 g, 86%) as a white foam.

<u>Synthesis of compound **91**</u>

To a solution of compound **90** (10.14 g, 19.3 mmol) in pyridine (50 mL) at 0°C was added methanesulfonyl chloride (2.69 mL, 34.8 mmol). The mixture was stirred at 0°C for 10 minutes, then at ambient temperature for 2 hours. The mixture was diluted with EtOAc (200 mL) and washed with water (2 x 50 mL). The combined aqueous portions were back-extracted with EtOAc (50 mL). The combined organics were washed with brine (2 x 50 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was dissolved in toluene and concentrated to give compound **91** (11.3 g, 97%) as a white foam which was used for the next reaction without further purification.

<u>Synthesis of compound **92**</u>

To a stirred mixture of diphenyl diselenide (7.04 g, 22.1 mmol) and EtOH

(100 mL) at 0°C, $NaBH_4$ (1.69 g, 44.2 mmol) was added portionwise over 7 minutes, then after 5 minutes the mixture was allowed to warm to ambient temperature and stirred for an additional hour. The resulting solution was added *via* cannula to a slurry of compound **91** in EtOH (175 mL), rinsing with EtOH (25 mL). The mixture was stirred at 50°C for 35 minutes. The mixture was cooled, water (70 mL) was added and the mixture was concentrated. The residue was dissolved in EtOAc (400 mL) and washed with water (100 mL), then brine (100 mL). The combined aqueous washes were back-extracted with EtOAc (3 x 75 mL). The combined organics were washed with brine (2 x 100 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc) to afford compound **92** (10.6 g, 87%) as a yellow foam.

Synthesis of compound **93**

A mixture of compound **92** (10.2 g, 15.4 mmol) and 30% H_2O_2 solution in THF (4500 mL) was stirred at ambient temperature for 50 minutes then at 65°C for 40 minutes. After cooling, the mixture was diluted with EtOAc (500 mL) and washed with brine (200 mL), then saturated $NaHCO_3$ solution (200 mL). The combined aqueous portions were back-extracted with EtOAc (2 x 100 mL). The combined organic portions were washed with brine (2 x 200 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 3:1; EtOAc) to afford compound **93** (5.86 g, 75%) as a white foam.

Synthesis of compound **94**

To a solution of compound **93** (4.81 g, 9.49 mmol) in THF (90 mL), ^{t}BuOH (30 mL) and water (9 mL) were added NMO (1.72 g, 14.2 mmol) and OsO_4 (3.0 mL of a 4% solution in water, 0.47 mmol). The reaction mixture was stirred at ambient temperature overnight, then a solution of $Na_2S_2O_3 \cdot 5H_2O$ (1.75 g) in water (30 mL) was added. The mixture was stirred for 30 minutes then diluted with brine (350 mL) and extracted with CH_2Cl_2 (200 mL, 2 x 125 mL, 75 mL). The combined organics were washed with brine (2 x 150 mL), dried over anhydrous $MgSO_4$ and concentrated to give compound **94** (5.70 g) as a light brown foam which was used for the next reaction

without further purification.

Synthesis of compound **95**

To a solution of compound **94** (5.70 g) in CH_2Cl_2 (100 mL) was added $Pb(OAc)_4$ (4.43 g, 9.49 mmol). The reaction mixture was stirred at ambient temperature for 35 minutes, then filtered through a silica plug and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 9:1, 4:1) to afford compound **95** (4.21 g, 85% from INT1660) as a white foam.

Synthesis of compound **96**

To a stirred solution of compound **95** (300 mg, 0.59 mmol) in a mixture of MeOH/THF (2mL/7mL) at 0°C was added $NaBH_4$ (45 mg, 1.2 mmol). After 5 min at 0°C, the mixture was stirred at ambient temperature and additional $NaBH_4$ (89 mg, 2.4 mmol) was added in portions over 4 hours. The mixture was cooled to 0°C and the reaction was quenched by water (1 mL). The mixture was diluted with EtOAc (200 mL), washed twice with brine, dried and concentrated. The residue was purified by column chromatography (hexanes/EtOAc, 6:4) to afford compound **96** in 82% yield.

Synthesis of compound **97**

Using the methods described in the Method B procedure in Example 12 below for the synthesis of compound **116**, compound **97** was prepared from compound **96**. The crude compound **97** was subjected to column chromatography (hexanes/EtOAc, 8:2), and used in next step without further purification.

Synthesis of compound **98**

To a stirred solution of impure compound **97** (0.59 mmol) in THF (20 mL) at 0°C was added 1M LAH in THF (5.8 mL, 5.8 mmol) dropwise. After 25 min at 0°C, the mixture was stirred at ambient temperature for 3 hours. The mixture was cooled to 0°C again and solid $Na_2SO_4 \cdot 10H_2O$ (1.86 g, 5.8 mmol) was added portionwise. The mixture was stirred at 0°C for 5 min and then at ambient temperature for another 20 min before filtration through Celite. The filtrate was concentrated and the residue was purified by column chromatography (EtOAc/MeOH/Et_3N, 9:1:0.5) to afford compound **98** (150 mg, 59% from compound **96**) as a clear gum.

Synthesis of compound **99**

A mixture of compound **98** (150 mg, 0.32 mmol) and 80% HOAc (5 mL) was stirred at 40°C for 7 hours. The solvents were removed by rotary evaporation and dried in vacuum. The crude compound **99** was used in next step without purification.

Synthesis of compound **100**

A mixture of $MePPh_3Br$ (1.26 g, 3.5 mmol) and KO^tBu (395 mg, 3.5 mmol) in THF (15 mL) was stirred at ambient temperature for 2 hours and then added to a mixture of compound **99** obtained above in THF (5 mL) and DMF (1 mL). The reaction mixture was stirred at ambient temperature for 2 days and then quenched with saturated NH_4Cl (0.25 mL). The mixture was diluted with EtOAc (20 mL) and MeOH (5 mL) and filtered through Celite. The filtrate was concentrated and the residue was purified by column chromatography (EtOAc/MeOH/water/Et_3N, 6:3:0.5:0.5) to yield compound **100** (47 mg, 47% from compound **98**).

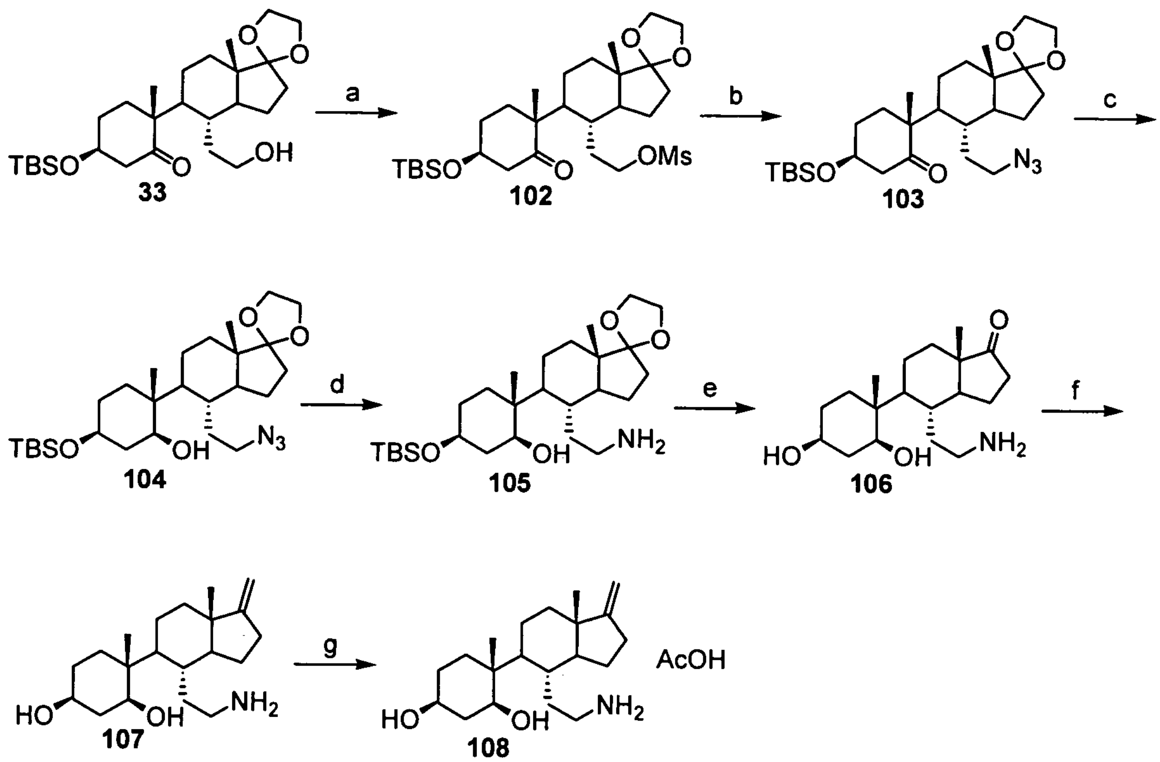
Synthesis of compound **101**

A solution of compound **100** (47 mg, 0.15 mmol) in 80% HOAc was stirred at ambient temperature for a few minutes and then the solvents were removed by rotary evaporation. The residue was co-evaporated with MeOH several times. The residue was dissolved in a small amount of MeOH and treated with a small amount of acetonitrile. The product was precipitated out and the supernatant was removed with pipette. The solid obtained was dried in vacuum to afford compound **101** (35 mg, 62%) as a pale powder: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 308.06; $C_{19}H_{34}NO_2$.

EXAMPLE 11

Compounds **107-108**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 11. Any number of compounds related to compounds **107-108** could be produced using similar methodology. Starting compound **33** may be prepared according to procedures described above in Example 3.

REACTION SCHEME 11



a) MsCl, pyridine; b) NaN_3, DMF, 40°C; c) $NaBH_4$, MeOH, THF; d) PPh_3, H_2O, THF, 40°C; e) 2 N HCl, THF; f) $MePPh_3Br$, KO^tBu, THF, DMF; g) 80% AcOH.

In general, the free hydroxyl is reacted to give the mesylate compound **102** using MsCl and pyridine. Azide displacement of the mesylate using sodium azide in DMF gives compound **103**. Sodium borohydride selectively reduces the carbonyl to give compound **104**. Reduction of the azide using PPh_3 and water in THF gives compound **105**. Treatment with HCl removes the TBS group and the cyclic ketal to give compound **106**. Olefination using $MePPh_3Br$ and KO^tBu in THF gives compound **107**. Treatment with acetic acid forms the ammonium acetate salt to give compound **108**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **102**</u>

To a solution of compound **33** (15.0 g, 31.2 mmol) in pyridine (100 mL) at 0°C was added methanesulfonyl chloride (4.35 mL, 56.2 mmol). The reaction mixture was stirred at 0°C for 10 minutes, then at ambient temperature for 4 hours. The mixture

was diluted with EtOAc (400 mL), washed with water (2 x 100 mL) and then brine (2 x 100 mL), then dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 3:1, 1:1) to give compound **102** (12.8 g, 78%) as a white foam.

Synthesis of compound **103**

A mixture of compound **102** (0.800 g, 1.43 mmol) and NaN_3 (0.190 g, 2.89 mmol) in dry DMF (15 mL) was stirred at 50°C for 3 hours, then at 40°C overnight. After cooling to ambient temperature, the mixture was diluted with water (80 mL) and extracted with Et_2O (3 x 30 mL). The organic portion was washed with brine (2 x 20 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes; hexanes/EtOAc, 19:1, 9:1, 4:1) to give compound **103** (0.476 g, 66%) as a yellow oil.

Synthesis of compound **104**

To a stirred solution of compound **103** (0.473 g, 0.935 mmol) in THF (15 mL) and MeOH (5 mL) at 0°C was added $NaBH_4$ (0.286 g, 7.48 mmol) in portions over 5 minutes. The resulting mixture was stirred at 0°C for 10 minutes then at ambient temperature overnight. The reaction was quenched with water (50 mL), then extracted with EtOAc (30 mL, 2 x 20 mL). The organic extracts were washed with brine (2 x 20 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 9:1, 4:1) to give compound **104** (0.349 g, 73%) as a white foam.

Synthesis of compound **105**

A mixture of compound **104** (0.346 g, 0.681 mmol), PPh_3 (0.542 g, 2.04 mmol), water (1 mL) and THF (20 mL) was stirred at 40°C overnight and then concentrated. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH, 19:1; CH_2Cl_2/MeOH/Et_3N, 9:1:0.2) to give compound **105** (0.336 g, quantitative) as a colourless glass.

Synthesis of compound **106**

A mixture of compound **105** (0.050 g, 0.10 mmol) and 2 N HCl (1 mL, 2

mmol) in THF (3 mL) was stirred at ambient temperature for 2 hours, then concentrated. To a solution of the residue in CH_2Cl_2/MeOH (1:1, 8 mL) was added macroporous polystyrene-bound carbonate (0.105 g, 0.300 mmol) and the mixture was stirred at ambient temperature for 3 hours. The mixture was filtered, rinsing with CH_2Cl_2/MeOH (1:1, 3 x 5 mL) and the filtrate was concentrated to give compound **106** (0.032 g, 94%) as a colourless oil.

Synthesis of compound **107**

A mixture of KO^tBu (0.339 g, 2.87 mmol) and $MePPh_3Br$ (1.02 g, 2.87 mmol) in THF (12 mL) was stirred at ambient temperature for 2.5 hours, then a solution of compound **106** (0.116 g, 0.359 mmol) in THF (6 mL) and DMF (2 mL) was added. The reaction mixture was stirred at ambient temperature overnight, then quenched with saturated NH_4Cl solution (4 mL), diluted with MeOH (10 mL), filtered and the filtrate was concentrated. The residue was washed with EtOAc (3 x 10 mL) and MeOH (2 x 10 mL). The combined washes were concentrated. The residue was purified by chromatography on silica gel (EtOAc/MeOH; EtOAc/MeOH/H_2O/Et_3N) to afford compound **107** (0.024 g, 21%) as a colourless glass.

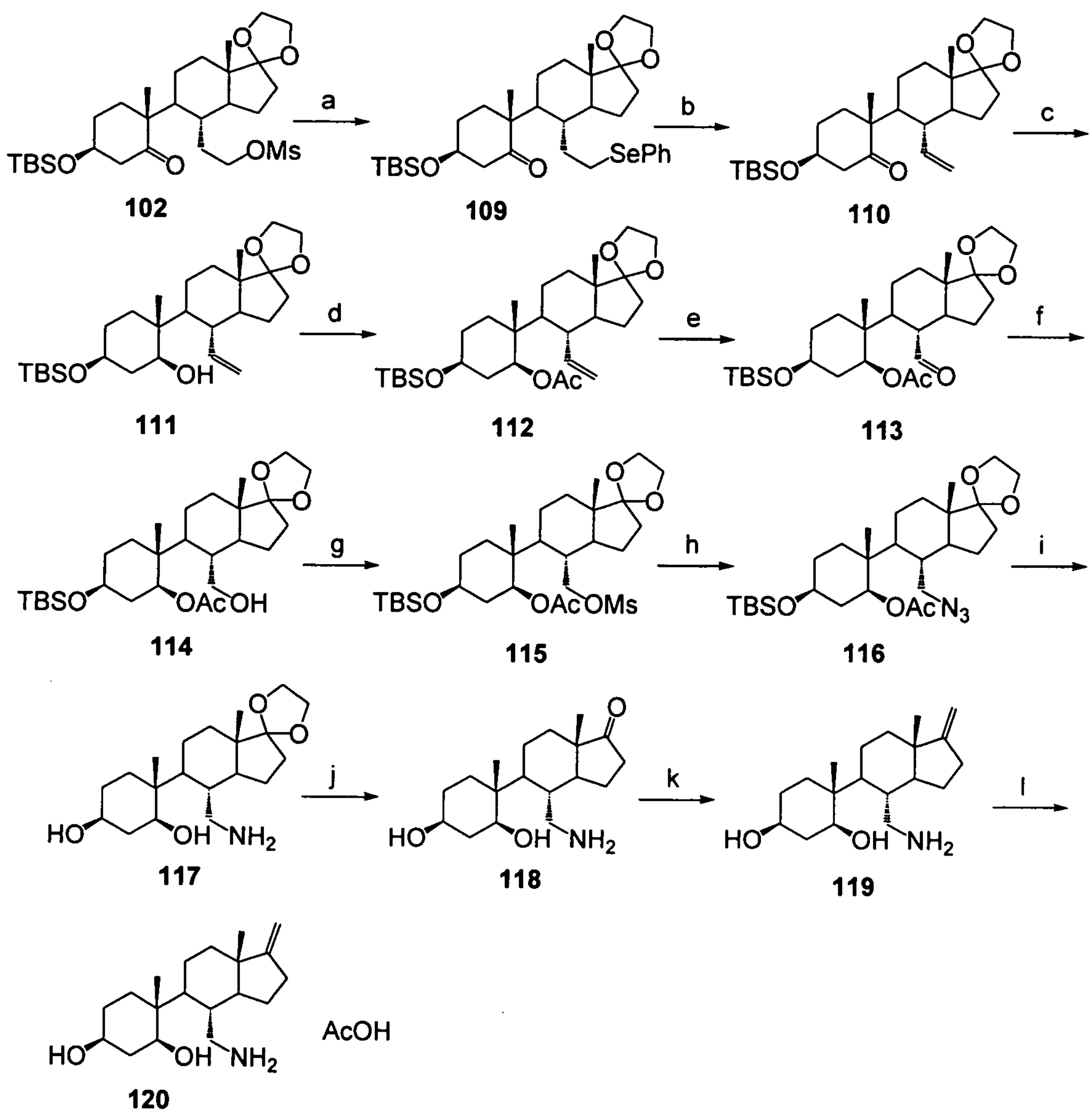
Synthesis of compound **108**

A mixture of compound **107** (0.035 g, 0.11 mmol) and 80% acetic acid (5 mL) was stirred at ambient temperature for 45 minutes, then concentrated. The residue was dissolved in MeOH and concentrated three times. Precipitation from ACN/MeOH gave compound **108** (0.036 g, 86%) as a yellow solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 322.24; $C_{20}H_{36}NO_2$.

EXAMPLE 12

Compounds **119-120**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 12. Any number of compounds related to compounds **119-120** could be produced using similar methodology. Starting compound **102** may be prepared according to procedures described above in Example 11.

REACTION SCHEME 12



a) $(SePh)_2$, $NaBH_4$, EtOH, 50°C; b) 30% H_2O_2, THF, 65°C; c) $NaBH_4$, MeOH, THF; d) Ac_2O, DMAP, pyridine; e) O_3, MeOH, CH_2Cl_2, -78°C; Me_2S; f) $NaBH_4$, MeOH/THF; g) MsCl, pyridine; h) NaN_3, DMF, 60°C; i) LAH, THF; j) 2N HCl, THF; k) $MePPh_3Br$, KO^tBu, THF; l) AcOH

In general, mesylate displacement by phenylselenide gives compound **109**. Oxidative elimination using hydrogen peroxide gives the olefin compound **110**. Sodium borohydride reduction gives the alcohol compound **111**. Reaction with acetic anhydride and DMAP in pyridine gives compound **112**. Ozonation gives the aldehyde compound **113**. Sodium borohydride reduction gives compound **114**. The free hydroxyl

is reacted to give the mesylate compound **115** using MsCl and pyridine. Azide displacement of the mesylate using sodium azide in DMF gives compound **116**. Reaction with lithium aluminum hydride in THF reduces the azide and removes both the acyl group and the TBS group to give compound **117**. Treatment with HCl removed the cyclic ketal to give compound **118**. Olefination using $MePPh_3Br$ and KO^tBu in THF gave compound **119**. Treatment with acetic acid forms the ammonium acetate salt to give compound **120**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **109**</u>

To a stirred mixture of diphenyl diselenide (7.25 g, 22.8 mmol) and EtOH (100 mL) at 0°C $NaBH_4$ (1.74 g, 45.5 mmol) was added portionwise, after 5 minutes the mixture was allowed to warm to ambient temperature and stirred for an additional hour. The resulting solution was added via cannula to a slurry of compound **102** in EtOH (175 mL), rinsing with EtOH (25 mL). The mixture was stirred at ambient temperature for 30 minutes then at 50°C for 45 minutes. The mixture was cooled, water (80 mL) was added and the mixture was concentrated. The residue was dissolved in EtOAc (500 mL) and washed with brine (2 x 100 mL). The combined aqueous washes were back-extracted with EtOAc (200 mL) and the EtOAc portion was washed with brine (2 x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 9:1) to afford compound **109** (8.9 g, 75%) as a light yellow solid.

<u>Synthesis of compound **110**</u>

A mixture of compound **109** (0.907 g, 1.46 mmol) and 30% H_2O_2 solution in THF (60 mL) was stirred at ambient temperature for 1 hour then at 65°C for 1 hour. After cooling, the mixture was diluted with EtOAc (60 mL) and washed with brine (30 mL), then saturated $NaHCO_3$ solution (40 mL). The combined aqueous portions were back-extracted with EtOAc (2 x 20 mL). The combined organic portions were washed with brine (2 x 40 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes; hexanes/EtOAc, 7:1) to afford

compound **110** (0.447 g, 66%) as a white solid.

Synthesis of compound **111**

To a stirred solution of compound **110** (3.82 g, 8.26 mmol) in THF (75 mL) and MeOH (25 mL) at 0°C was added $NaBH_4$ (1.06 g, 27.7 mmol) in portions over 20 minutes. The resulting mixture was stirred at 0°C for 10 minutes, then at ambient temperature overnight. The reaction was cooled to 0°C and quenched with water (200 mL), then extracted with EtOAc (3 x 100 mL). The organic extracts were washed with brine (2 x 100 mL), dried over anhydrous $MgSO_4$ and concentrated to afford compound **111** (3.76 g, 98%) as a white foam.

Synthesis of compound **112**

To a solution of compound **111** (5.36 g, 11.5 mmol) and DMAP (0.282 g, 2.31 mmol) in pyridine (85 mL) was added acetic anhydride (10.9 mL, 115 mmol). The resulting mixture was stirred at 50°C overnight, then cooled to ambient temperature, diluted with EtOAc (350 mL) and washed with water (120 mL). The aqueous portion was back-extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine (2 x 125 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 9:1) to afford compound **112** (5.37 g, 92%) as a white foam.

Synthesis of compound **113**

A solution of compound **112** (4.84 g, 9.55 mmol) in CH_2Cl_2 (75 mL) and MeOH (25 mL) was treated with ozone at -78°C for 3.5 hours. Nitrogen was bubbled at -78°C for 10 minutes, then dimethyl sulfide (12 mL, 164 mmol) was added and the mixture was stirred at -78°C for 10 minutes, then at ambient temperature for 2 hours. The mixture was concentrated, then the residue was dissolved in EtOAc (200 mL), washed with water (2 x 50 mL) and then brine (2 x 50 mL), dried over anhydrous $MgSO_4$ and concentrated to afford compound **113** (4.59 g, 94%) as a white foam.

Synthesis of compound **114**

To a stirred solution of compound **113** (300 mg, 0.59 mmol) in a mixture of MeOH/THF (2mL/7mL) at 0°C was added $NaBH_4$ (64 mg, 1.7 mmol). After 15 min at

0°C, the mixture was stirred at ambient temperature for 1 hour and then additional $NaBH_4$ (20 mg, 0.53 mmol) was added. The mixture was stirred for another 50 min before cooled to 0°C and the reaction was quenched by water (5 mL). The mixture was diluted with EtOAc (200 mL), washed twice with brine, dried and concentrated to afford crude compound **114** (299 mg, 99%). The product was used in next step without purification.

<u>Synthesis of compound **115**</u>

To a stirred solution of compound **114** (103 mg, 0.2 mmol) in pyridine at 0°C was added MsCl (0.1 mL, 0.9 mmol) dropwise. The resulting mixture was stirred at ambient temperature for 8 hours, then diluted with EtOAc (200 mL), washed with brine, dried and concentrated to give crude compound **115**, which was used in next step without purification.

<u>Synthesis of compound **116**</u>

Method A

A mixture of compound **115** obtained above and NaN_3 (46 mg, 0.7 mmol) in DMF (1.6 mL) was stirred at 60°C overnight. The reaction mixture was diluted with toluene (150 mL) and washed with brine. The aqueous washings were combined and extracted with toluene. The organic extracts were combined and washed with brine, dried and concentrated. The residue was purified by column chromatography on silica gel (hexanes/EtOAc, 9:1) to afford compound **116** (45 mg, 43% from INT1861) as a pale gum.

Method B

To a stirred solution of compound **114** (293 mg, 0.57 mmol) in THF (6 mL) at 0°C were added Ph_3P (329 mg, 1.25 mmol), DIAD (0.25 mL, 1.27 mmol), and DPPA (0.27 mL, 1.25 mmol). After 10 min at 0°C, the mixture was stirred at ambient temperature overnight. The reaction was quenched by water (20 mL), and extracted with EtOAc. The EtOAc extracts were combined and washed with saturated $NaHCO_3$, brine, dried and concentrated. The residue was purified by column chromatography

(hexanes/EtOAc, 9:1) to yield compound **116** (275 mg, 89%) as a pale gum.

Synthesis of compound **117**

To a stirred solution of compound **116** (128 mg, 0.24 mmol) in THF (5 mL) at 0°C was added 1M LAH in THF (0.95 mL, 0.95 mmol) dropwise. After 10 min at 0°C, the mixture was stirred at ambient temperature for 4.5 hours. The mixture was cooled to 0°C again and solid $Na_2SO_4.10H_2O$ (308 mg, 0.95 mmol) was added portionwise. The mixture was stirred at 0°C for 10 min and then at ambient temperature for another 20 min before filtration through Celite. The filtrate was diluted with EtOAc (200 mL), washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (EtOAc/MeOH/water/Et_3N, 7:2:0.5:0.5) to afford compound **117** (45 mg, 53%).

Synthesis of compound **118**

A mixture of compound **117** (45 mg, 0.13 mmol) and 2N HCl (1 mL) in THF (3 mL) was stirred at ambient temperature overnight. The solvents were removed by rotary evaporation and the residue was purified by column chromatography (EtOAc/MeOH/water/Et_3N, 7:2:0.5:0.5) to give compound **118** (50 mg, with traces of Et_3N).

Synthesis of compound **119**

A mixture of $MePPh_3Br$ (457 mg, 1.28 mmol) and KO^tBu (144 mg, 1.28 mmol) in THF (6 mL) was stirred at ambient temperature for 1 hour 40 min and then added to a mixture of compound **118** (50 mg, 0.16 mmol) in THF (3 mL) and DMF (1 mL). The reaction mixture was stirred at ambient temperature overnight and then quenched with saturated NH_4Cl (2 mL). After being stirred for a few minutes, the mixture was concentrated by rotary evaporation. The residue paste was repeatedly extracted with EtOAc and filtered. The filtrates were combined and concentrated. The residue was purified by column chromatography (EtOAc/MeOH/water/Et_3N, 7:2:0.5:0.5) to yield compound **119** (24 mg, 63% from compound **117**).

Synthesis of compound **120**

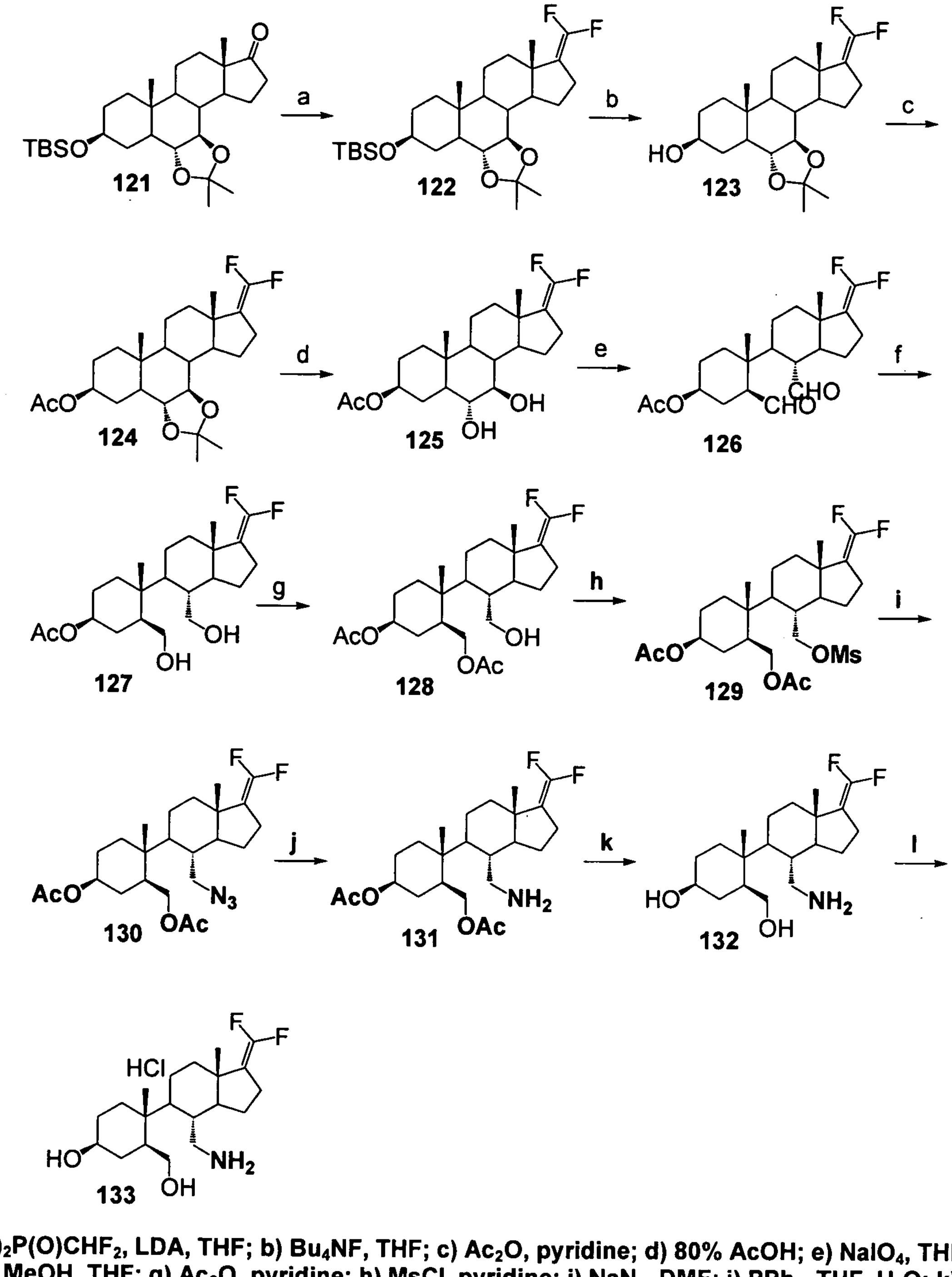
To a stirred solution of compound **119** (43 mg) in MeOH (~2 mL) was

added 80% HOAc (0.5 mL) and then the mixture was concentrated to dryness. The residue was re-dissolved in a small amount of MeOH and treated with a small amount of acetonitrile. The mixture was concentrated again and the resulting precipitate was dried in vacuum to afford compound **120** (53 mg, 100%) as a pale powder: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 308.11; $C_{19}H_{34}NO_2$.

EXAMPLE 13

Compounds **132-133**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 13. Any number of compounds related to compounds **132-133** could be produced using similar methodology. The starting compound **121** was prepared according to the procedures described in U.S. Patent 6,046,185.

REACTION SCHEME 13



a) $(EtO)_2P(O)CHF_2$, LDA, THF; b) Bu_4NF, THF; c) Ac_2O, pyridine; d) 80% AcOH; e) $NaIO_4$, THF; f) $NaBH_4$, MeOH, THF; g) Ac_2O, pyridine; h) MsCl, pyridine; i) NaN_3, DMF; j) PPh_3, THF, H_2O; k) NaOMe, MeOH; l) HCl, MeCN, MeOH.

In general, olefination using $(EtO)_2P(O)CHF_2$ and lithium diisopropylamide (LDA) in THF gives compound **122**. Tetrabutylammonium fluoride in THF removes the

TBS group to give compound **123**. Reaction with acetic anhydride in pyridine gives compound **124**. Treatment with 80% acetic acid removes the acetonide group to give compound **125**. $NaIO_4$ oxidation gives the dialdehyde compound **126**. Sodium borohydride reduction gives compound **127**. Reaction with acetic anhydride in pyridine gives compound **128**. The free hydroxyl is reacted to give the mesylate compound **129** using MsCl and pyridine. Azide displacement of the mesylate using sodium azide in DMF gives compound **130**. Reduction of the azide using PPh_3 and water in THF gives compound **131**. Methanolysis of the acetates gives compound **132**. Treatment with HCl forms the salt compound **133**.

Following are specific examples of the compounds prepared above.

Synthesis of compound **122**

Freshly prepared LDA (3.4 mL, 2.4 mmol) was added to a -78°C solution of $F_2CHPO(OEt)_2$ (0.40 mL, 2.5 mmol) in dry THF (3 mL) under argon. After 20 minutes, a solution of compound **121** (0.30 g, 0.63 mmol) in dry THF was added. The reaction was continued for 1 hour, then slowly warmed to ambient temperature over 2 hours and finally was heated at 60°C for 3 hours. The reaction was cooled to ambient temperature, then quenched by 0.5 mL of water. The solution was diluted with EtOAc and was washed with brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (4% EtOAc/hexanes) to afford compound **122** (0.145 g, 45%) as a white solid.

Synthesis of compound **123**

A solution of compound **122** (0.65 g, 1.3 mmol), Bu_4NF (2.7 ml of a 1M solution in THF) and THF (10 ml) was heated at 50°C for 3 hours. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (30% EtOAc/hexanes) to afford compound **123** (0.54 g, quantitative).

Synthesis of compound **124**

A solution of compound **123** (0.54 g, 1.3 mmol), acetic anhydride (0.24 mL, 2.5 mmol) and pyridine (5 mL) was stirred at ambient temperature for 3 days. The solution was diluted with EtOAc, was washed with brine, then dried over $MgSO_4$, filtered

and concentrated. The crude compound **124** was used in the next step without further purification.

Synthesis of compound **125**

A solution of compound **124** (crude, 1.3 mmol) and 80% acetic acid (10 mL) was heated at 50°C for 2 hours. The reaction mixture was concentrated under reduced pressure and the residual solvents were removed by codistillation with toluene. The crude compound **125** was used in the next step without further purification.

Synthesis of compound **126**

A solution of $NaIO_4$ (0.54 g, 2.5 mmol) and water (4 mL) was added to a solution of compound **125** (crude, 1.3 mmol) and THF (10 mL). After 3 hours the solution was diluted with CH_2Cl_2 and washed with brine, then dried over $MgSO_4$, filtered and concentrated. The crude compound **126** was used in the next step without further purification.

Synthesis of compound **127**

Sodium borohydride (48 mg, 1.3 mmol) was added to a solution of compound **126** (crude, 1.3 mmol), THF (6 mL) and MeOH (2 mL). After 3 hours, the reaction was quenched by water (15 mL) and the solution was extracted using 2 x 15 mL of EtOAc. The combined extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (30% EtOAc/hexanes) to afford compound **127** (0.38 g, 75%) as a white solid.

Synthesis of compound **128**

A solution of compound **127** (0.38 g, 0.95 mmol), acetic anhydride (0.09 mL, 1 mmol) and pyridine (5 mL) was stirred overnight at ambient temperature. The reaction mixture was diluted with water and extracted with 2 x 15 mL of EtOAc. The combined extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel to afford compound **128** (0.32 g, 76%) as a white solid.

Synthesis of compound **129**

A solution of compound **128** (0.32 g, 0.72 mmol), MsCl (0.11 mL, 1.4 mmol) and pyridine (5 mL) was stirred at ambient temperature for 3 hours. The reaction mixture was quenched with water and was extracted with EtOAc (2 x 25 mL). The combined extracts were washed with brine then were dried over $MgSO_4$, filtered and concentrated. The crude compound **129** was used in the next step without further purification.

Synthesis of compound **130**

A solution of compound **129** (crude, 0.72 mmol), NaN_3 (0.83 g, 3.6 mmol) and DMF (5 mL) was heated overnight at 55°C. The reaction mixture was cooled to ambient temperature and was diluted with water (10 mL), then extracted with toluene. The toluene solution was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (20% EtOAc/hexanes) to afford compound **130** (0.30 g, 89%) as a white foam.

Synthesis of compound **131**

A solution of compound **130** (0.13 g, 0.28 mmol), PPh_3 (0.15 g, 0.56 mmol), THF (3 mL) and water (0.3 mL) was stirred under argon for 3 days. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel (EtOAc/MeOH/Et_3N 9:1:0.5) to afford compound **131** (98 mg, 79%) as a white solid.

Synthesis of compound **132**

A solution of compound **131** (0.28 g, 0.65 mmol), NaOMe (0.5 mL of a 25% solution in MeOH) and MeOH (5 mL) was stirred at ambient temperature for 3 hours. The reaction mixture was concentrated and the residue was purified by column chromatography (EtOAc/MeOH/NH_4OH 9:1:0.6) to afford compound **132** (0.21 g, 89%) as a white solid.

Synthesis of compound **133**

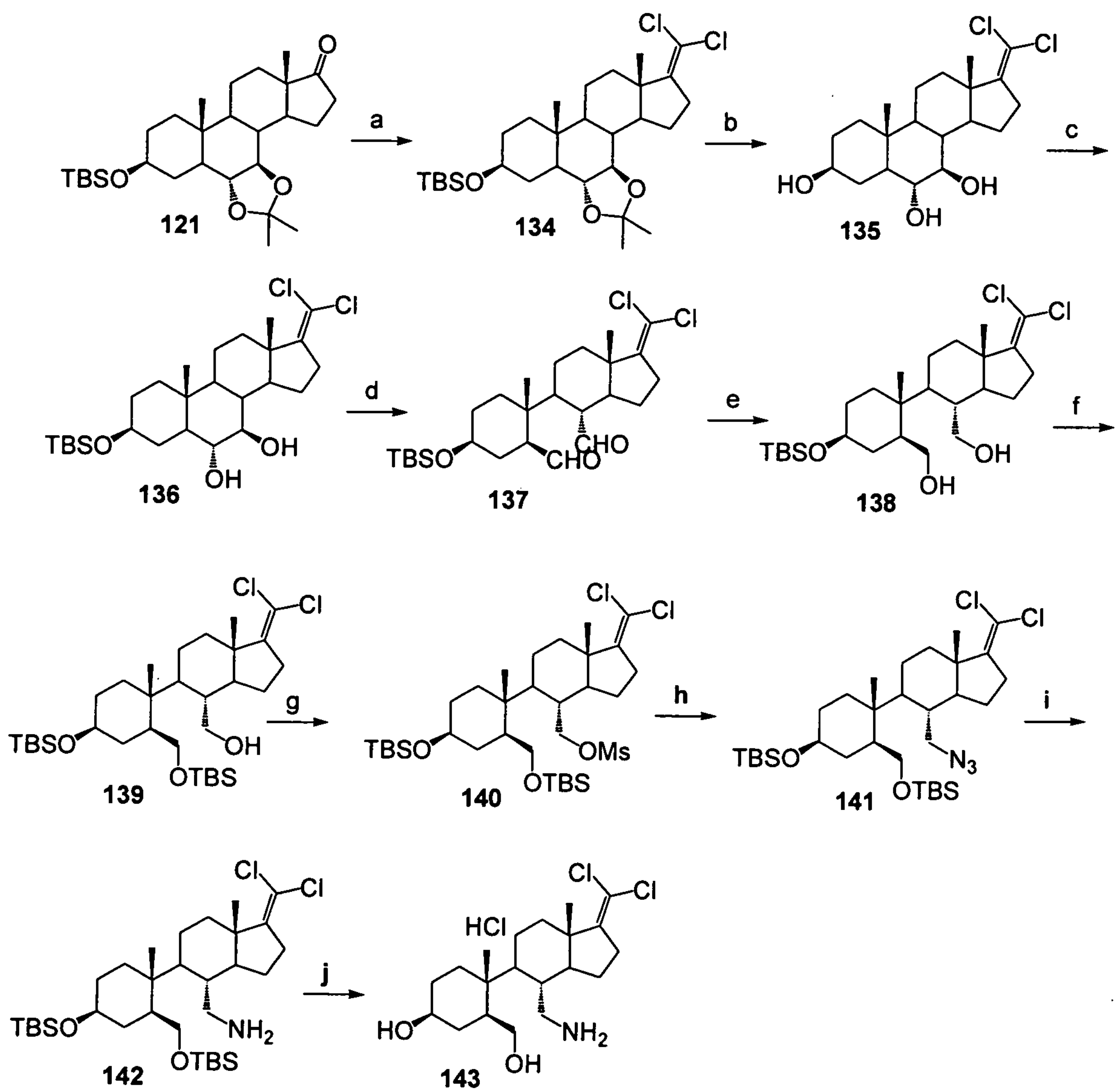
A solution of compound **132** (0.24 g, 0.68 mmol), HCl (1.36 mL of a 1M solution in Et_2O) and MeOH (3 mL) was stirred at ambient temperature for 30 minutes.

The reaction mixture was concentrated and the residue was triturate in EtOAc (5 mL). The resulting white solid was filtered and dried overnight under high vacuum at 56°C to afford compound **133** (0.21 g, 78%): LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 358.14; $C_{20}H_{34}F_2NO_2$.

EXAMPLE 14

Compound **143**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 14. Any number of compounds related to compound **143** could be produced using similar methodology. Starting compound **121** may be prepared by the procedures described in U.S. Patent 6,046,185.

REACTION SCHEME 14



a) $(EtO)_2P(O)CCl_3$, LDA, THF; b) 80% AcOH; c) TBSCl, Imidazole, DMF; d) $NaIO_4$, THF; e) $NaBH_4$, MeOH, THF; f) TBSCl, Imidazole, DMF; g) MsCl, pyridine; h) NaN_3, DMF; i) PPh_3, THF, H_2O; j) HCl, THF, H_2O.

In general, olefination using $(EtO)_2P(O)CCl_3$ and LDA in THF gives compound **134**. Treatment with 80% acetic acid removes both the TBS group and the acetonide group to give compound **135**. Treatment with TBSCl and imidazole in DMF selectively protects one hydroxyl to give compound **136**. $NaIO_4$ oxidation gives the dialdehyde compound **137**. Sodium borohydride reduction gives compound **138**.

Treatment with TBSCl and imidazole in DMF selectively protects one hydroxyl to give compound **139**. The free hydroxyl is reacted to give the mesylate compound **140** using MsCl and pyridine. Azide displacement of the mesylate using sodium azide in DMF gives compound **141**. Reduction of the azide using PPh_3 and water in THF gives compound **142**. Treatment with HCl removes the TBS groups and forms the salt compound **143**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **134**</u>

$CCl_3P(O)(OEt)_2$ (1.12 ml, 6 mmol) was added to a -78°C solution of freshly prepared LDA (6 mmol) in dry THF (20 mL) under argon. After 5 minutes a compound **121** (954 mg, 2 mmol) was added. The reaction was continued for 1 hour, then slowly warmed to ambient temperature over 2 hours and finally was stirred at ambient temperature for overnight. The reaction quenched by 0.5 mL of water. The solution was diluted with EtOAc and was washed with water, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (3% EtOAc/hexanes) to afford compound **134** (109 mg, 10%) as a pale yellow foam.

<u>Synthesis of compound **135**</u>

A solution of compound **134** (288 mg, 0.53 mmol) in 2 ml THF and 80% acetic acid (8 mL) was heated at 50°C for 2 hours. The reaction mixture was concentrated under reduced pressure and the residual solvents were removed by codistillation with toluene. The crude compound **135** was used in the next step without further purification.

<u>Synthesis of compound **136**</u>

A solution of compound **135** (crude, 0.53 mmol) in DMF (3 mL), imidazole (108 mg, 1.6 mmol) and TBSCl (160 mg, 1.1 mmol) was stirred at ambient temperature for 2 hours. The reaction mixture was diluted with 50 ml water and extracted with 100 mL of EtOAc. The extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel to afford compound **136** (243 mg, 91%) as a pale yellow foam.

Synthesis of compound **137**

A solution of $NaIO_4$ (205 mg, 0.96 mmol) and water (2 mL) was added to a solution of compound **136** (243 mg, 0.48 mmol) and THF (6 mL). After 3 hours the solution was diluted with CH_2Cl_2 and washed with brine, then dried over $MgSO_4$, filtered and concentrated. The crude compound **137** was used in the next step without further purification.

Synthesis of compound **138**

Sodium borohydride (36 mg, 0.96 mmol) was added to a solution of compound **137** (crude, 0.48 mmol), THF (3 mL) and MeOH (1 mL). After 3 hours, the reaction was quenched by water (30 mL) and the solution was extracted using 2 x 50 mL of EtOAc. The combined extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (30% EtOAc/hexanes) to afford compound **138** (201 mg, 83%) as pale yellow oil.

Synthesis of compound **139**

A solution of compound **138** (201 mg, 0.4 mmol), imidazole (136 mg, 2 mmol), TBSCl (110 mg, 0.73 mmol) and DMF (3 mL) was stirred for 1 hour at ambient temperature. The reaction mixture was diluted with 30 mL water and extracted with 2 x 40 mL of EtOAc. The combined extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel to afford compound **139** (230 mg, 93%) as pale yellow oil.

Synthesis of compound **140**

A solution of compound **139** (216 mg, 0.35 mmol), MsCl (0.14 mL, 1.8 mmol) and pyridine (3.5 mL) was stirred at ambient temperature for 2 hours. The reaction mixture was quenched with 30 mL water and was extracted with EtOAc (2 x 40 mL). The combined extracts were washed with brine then were dried over $MgSO_4$, filtered and concentrated. The crude compound **140** was used in the next step without further purification.

Synthesis of compound **141**

A solution of compound **140** (crude, 0.35 mmol), NaN_3 (178 mg, 2.7 mmol)

and DMF (3 mL) was heated overnight at 55°C. The reaction mixture was cooled to ambient temperature and was diluted with water (30 mL), then extracted with toluene. The toluene solution was dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (5% EtOAc/hexanes) to afford compound **141** (202 mg, 89%) as pale yellow oil.

Synthesis of compound **142**

A solution of compound **141** (202 mg, 0.31 mmol), PPh_3 (320 mg, 1.2 mmol), THF (4 mL) and water (0.3 mL) was stirred under argon overnight, then heated at 50°C for 4 hours. The reaction mixture was concentrated and the residue was purified by 2 g SCX ion-exchange (6 volume MeOH, 3 volume 5% ammonia/MeOH) to afford compound **142** as a pale yellow foam (TBS group lost partially during this process).

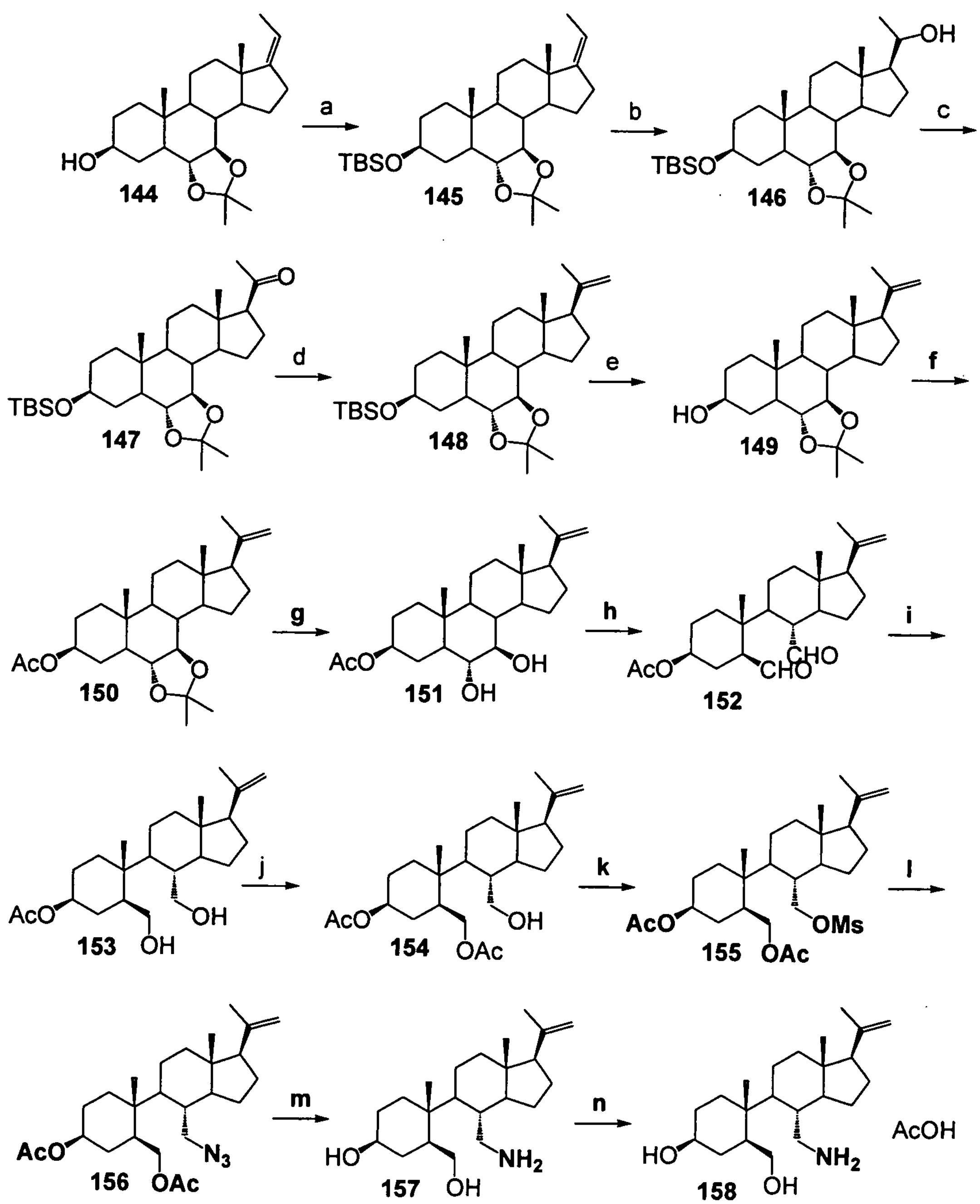
Synthesis of compound **143**

A solution of compound **142** (crude, 0.31 mmol), HCl (1 mL of a 1M solution in Et_2O), THF (3 mL) and water (0.5 mL) was stirred at ambient temperature for 2 hours. The reaction mixture was kept at 4°C for 1 hour. The resulting white solid was filtered and washed with EtOAc, then dried overnight under high vacuum at 56°C to afford compound **143** (122 mg, 92%): LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 390.06; $C_{20}H_{34}Cl_2NO_2$.

EXAMPLE 15

Compounds **157-158**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 15. Starting compound **144** may be prepared according to the procedures outlined in U.S. Patent 6,046,185. Any number of compounds related to compounds **157-158** could be produced using similar methodology.

REACTION SCHEME 15



a) TBSCl, imidazole, DMF; b) $BH_3 \cdot THF$, H_2O_2, THF; c) n-$Pr_4N(RuO_4)$, NMO, 4Å molecular sieves, CH_2Cl_2; d) $MePPh_3Br$, KO^tBu, THF; e) n-Bu_4NF, THF; f) Ac_2O, DMAP, pyridine; g) 80% AcOH; h) $NaIO_4$, THF, H_2O; i) $NaBH_4$, MeOH, THF; j) Ac_2O, DMAP, pyridine; k) MsCl, pyridine; l) NaN_3, DMF; m) $LiAlH_4$, THF; n) 80% AcOH.

In general, reaction of compound **144** with TBSCl and imidazole in DMF gives compound **145**. Hydroboration with borane-tetrahydrofuran complex in THF,

followed by oxidative workup with NaOH and H_2O_2 converts compound **145** to the secondary alcohol compound **146**. Oxidation with a catalytic amount of tetra-*n*-propylammonium perruthenate (TPAP) and NMO in CH_2Cl_2 gives compound **147.** Olefination with $MePPh_3Br$ and KO^tBu in THF gives alkene **148**. Tetrabutylammonium fluoride removes the TBS group to give compound **149**. Reaction with acetic anhydride in pyridine gives compound **150**. Treatment with 80% acetic acid removes the acetonide group to give compound **151**. $NaIO_4$ oxidation gives the dialdehyde compound **152**. Sodium borohydride reduction gives compound **153**. Reaction with acetic anhydride in pyridine selectively protects one hydroxyl to give compound **154**. The free hydroxyl is reacted to give the mesylate compound **155** using MsCl and pyridine. Azide displacement of the mesylate using sodium azide in DMF gives compound **156**. Reaction with lithium aluminum hydride in THF reduces the azide and removes the acetates to give compound **157**. Treatment with 80% acetic acid forms the ammonium acetate salt compound **158**.

<u>Synthesis of compound **145**</u>

A solution of compound **144** (10.0 g, 26.7 mol), TBSCl (6.22 g, 40.1 mmol), and imidazole (3.67 g, 53.4 mmol) in dry DMF (178 mL) was stirred at ambient temperature for 2.5 hours. The reaction mixture was diluted with water (250 mL) and extracted with toluene (3 x 250 mL). The combined toluene extracts were washed with brine (250 mL), dried over $MgSO_4$, filtered, and concentrated. The crude compound **145** (12.5 g, 96%) was used in the next reaction without further purification.

<u>Synthesis of compound **146**</u>

To a solution of compound **145** (12.5 g, 25.6 mmol) in dry THF (150 mL) was added borane-tetrahydrofuran complex (46 mL of 1.0 M solution in THF) and the reaction mixture was stirred at ambient temperature for 1 hour. 10% aqueous NaOH (180 mL) was slowly added. The mixture was cooled in ice and 30% aqueous solution of H_2O_2 (120 mL) was slowly added. The mixture was stirred at ambient temperature for 1 hour and then extracted with EtOAc (3 x 250 mL). The combined EtOAc extracts were washed with 10 % aqueous $Na_2S_2O_3$ (200 mL), brine (200 mL), dried over $MgSO_4$,

filtered, and concentrated. The residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc, 95:5 then 85:15 and hexanes/EtOAc, 90:10 then 85:15) to afford compound **146** (10.7 g, 83%) as a white solid.

<u>Synthesis of compound **147**</u>

To a mixture of compound **146** (8.50 g, 16.8 mmol), NMO (2.23 g, 18.5 mmol), 4Å molecular sieves (5.3 g) in CH_2Cl_2 (85 mL) was added TPAP (152 mg, 0.42 mmol). The reaction mixture was stirred at ambient temperature for 1 hour, then filtered through silica gel packed in a sintered glass funnel (eluted with hexanes/EtOAc, 1:1), and concentrated to dryness. The crude product **147** was used in the next reaction without further purification.

<u>Synthesis of compound **148**</u>

A mixture of KO^tBu (5.69 g, 48.1 mmol) and $MePPh_3Br$ (17.2 g, 48.1 mmol) in THF (160 mL) was stirred at ambient temperature for one hour under argon then compound **147** (8.10 g, 16.1 mmol) was added. The reaction mixture was stirred at ambient temperature for 4 hours, diluted with brine (150 mL), extracted with EtOAc (3 x 200 mL). The combined EtOAc extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 96:4 then 10:1 then 4:1) to afford compound **148** (6.3 g, 79%) as a white foam.

<u>Synthesis of compound **149**</u>

A solution of compound **148** (6.3 g, 12.5 mmol) and *n*-Bu_4NF (18.8 mL of a 1.0 M solution in THF) in THF (125 mL) was refluxed under argon for 1 hour. Solvent was evaporated under reduced pressure and the residue was purified by chromatography on silica gel (hexanes/EtOAc, 2:1 then 1:1) to afford compound **149** (4.8 g, 99%) as a white solid.

<u>Synthesis of compound **150**</u>

A solution of compound **149** (4.8 g, 12.4 mmol), acetic anhydride (2.3 mL, 24.7 mmol) and DMAP (151 mg, 1.24 mmol) in pyridine (60 mL) was stirred at ambient temperature overnight. The reaction mixture was diluted with EtOAc (300 mL) and

washed with brine (2 x 100 mL). The EtOAc layer was dried over $MgSO_4$, filtered, and concentrated. The crude compound **150** was used directly in the next step.

Synthesis of compound **151**

A mixture of compound **150** (crude, 12.4 mmol) and 80% acetic acid (90 mL) was stirred at 40°C for 1 hour. The solution was concentrated to afford compound **151** that was used in the next step without further purification.

Synthesis of compound **152**

A solution of compound **151** (2.20 g, 5.63 mmol), $NaIO_4$ (2.43 g, 11.3 mmol), water (23 mL) and THF (46 mL) was stirred at ambient temperature for 3 hours. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with brine (3 x 75 mL). The CH_2Cl_2 layer was dried over $MgSO_4$, filtered, and concentrated to afford compound **152** that was used in the next step without further purification.

Synthesis of compound **153**

A solution of compound **152** (crude, 5.63 mmol), $NaBH_4$ (538 mg, 14.1 mmol), THF (36 mL) and MeOH (12 mL) was stirred at 0°C for 10 minutes then at ambient temperature for 2 hours. The mixture was cooled in ice and 80% acetic acid (23 mL) was slowly added. The solution was stirred at ambient temperature for 10 minutes, then diluted with EtOAc (200 mL) and washed with brine (3 x 75 mL). The EtOAc layer was dried over $MgSO_4$, filtered, and concentrated to afford crude compound **153** that was used in the next step without further purification.

Synthesis of compound **154**

A solution of compound **153** (crude, 5.63 mmol), acetic anhydride (0.58 mL, 6.20 mmol) and DMAP (69 mg, 0.56 mmol) in pyridine (22 mL) was stirred at ambient temperature for 1.5 hours. The reaction mixture was diluted with EtOAc (200 mL) and washed with brine (3 x 75 mL). The EtOAc layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 5:1 then 4:1 then 7:3) to afford compound **154** (1.6 g, 65% for 5 steps).

Synthesis of compound **155**

To a solution of compound **154** (1.60 g, 3.68 mmol) in pyridine (15 mL) was added methanesulfonyl chloride (0.600 mL, 7.37 mmol) and the reaction mixture was stirred at ambient temperature for 4 hours. The solution was diluted with EtOAc (200 mL) and washed with brine (3 x 70 mL), then dried over $MgSO_4$, filtered, and concentrated to afford crude compound **155** that was used for the next reaction without further purification.

Synthesis of compound **156**

A mixture of compound **155** (crude, 3.68 mmol) and NaN_3 (479 mg, 7.36 mmol) in DMF (25 mL) was heated under argon at 60°C overnight. After cooling, the reaction mixture was diluted with toluene (300 mL) and was washed with brine (3 x 75 mL), then dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 9:1 then 8:2) to afford compound **156** (1.6 g, 95% for 2 steps) as a white foam.

Synthesis of compound **157**

A solution of $LiAlH_4$ (13.9 mL of a 1.0 M solution in THF) was added to an ice cooled solution of compound **156** (1.60 g, 13.9 mmol) in THF (35 mL) and stirred for 15 minutes. The stirring was continued at ambient temperature for 3 hours. The reaction mixture was cooled in ice, quenched with $Na_2SO_4 \cdot 10H_2O$ and stirred for 10 minutes. The mixture was then stirred for an additional 30 minutes at ambient temperature, diluted with EtOAc, and then filtered. The filtrate was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel (EtOAc/MeOH/H_2O/Et_3N, 70:20:10:0 then 70:20:10:3) to afford compound **157** (0.8 g, 66%) as a white solid.

Synthesis of compound **158**

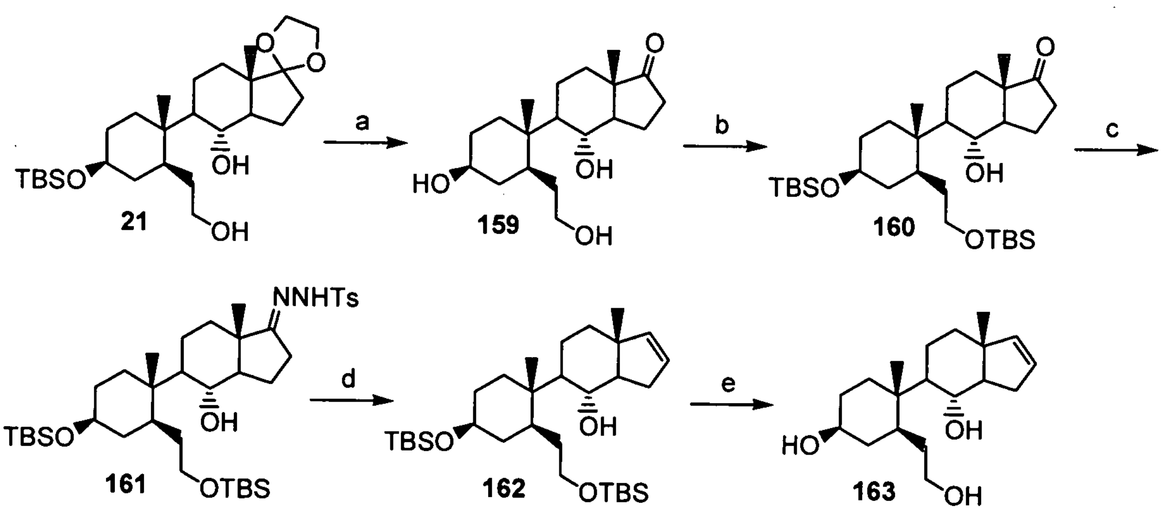
A solution of compound **157** (0.800 g, 2.29 mmol) and 80% acetic acid (20 mL) was heated at 40°C for 1 hour and, then concentrated. Residual solvent was removed by codistillation with acetonitrile. The residue was triturated in diethyl ether and filtered to give compound **158** (700 mg, 75%) as a white solid. LC/MS (direct

infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 350.12; $C_{22}H_{40}NO_2$.

EXAMPLE 16

Compound **163**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 16. Any number of compounds related to compound **163** could be produced using similar methodology. Starting compound **21** may be prepared according to the procedures described above in Example 1.

REACTION SCHEME 16



a) 80% AcOH, 55°C; b) TBSCl, imidazole, DMF; c) $TsNHNH_2$, toluene, reflux; d) LDA, THF; e) 80% AcOH

In general, treatment with 80% acetic acid removes the TBS group to give compound **159**. Reaction with TBSCl and imidazole in DMF gives compound **160**. Reaction with tosylhydrazine in toluene gives compound **161**. Reaction with LDA gives the elimination product compound **162**. Treatment with 80% acetic acid removes the TBS groups to give compound **163**.

<u>Synthesis of compound **159**</u>

A mixture of compound **21** (1.19 g, 2.46 mmol) and 80% acetic acid (20 mL) was stirred at 55°C for 3 hours then concentrated. The residue was dissolved in

toluene and concentrated three times. The residue was purified by chromatography on silica gel (EtOAc/MeOH, 49:1) to give compound **159** (0.747 g, 93%) as a white foam.

Synthesis of compound **160**

A mixture of compound **159** (0.747 g, 2.30 mmol), TBSCl (2.08 g, 13.8 mmol) and imidazole (1.88 g, 27.6 mmol) in dry DMF (12 mL) was stirred at ambient temperature for 3 hours then diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 7:3) to give compound **160** (1.11 g, 93%) as a white foam.

Synthesis of compound **161**

A mixture of compound **160** (0.500 g, 0.904 mmol) and $TsNHNH_2$ (0.236 g, 1.27 mmol) in toluene (20 mL) was heated at reflux for 1 hour, then stirred at ambient temperature overnight, then heated at reflux for another hour. After cooling, the mixture was concentrated. To the residue was added CH_2Cl_2 and the mixture was cooled in ice. The precipitate was filtered out, washing with cold CH_2Cl_2, then dried to afford compound **161** (0.588 g, 90%) as a white solid.

Synthesis of compound **162**

LDA solution was prepared by adding ^{n}BuLi (2 mL of a 2.5 M solution in hexanes, 5.0 mmol) to a solution of $^{i}Pr_2NH$ (0.77 mL, 5.5 mmol) in THF (4.23 mL) at 0°C, then stirring the solution at 0°C for 30 minutes. To a solution of compound **161** (0.550 g, 0.763 mmol) in THF (4 mL) at ambient temperature was added LDA solution (6.4 mL of a 0.71 M solution, 4.6 mmol). The reaction mixture was stirred at ambient temperature overnight. The mixture was diluted with brine (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 19:1, 9:1) to give compound **162** (0.062 g, 15%) as a yellow gel.

Synthesis of compound **163**

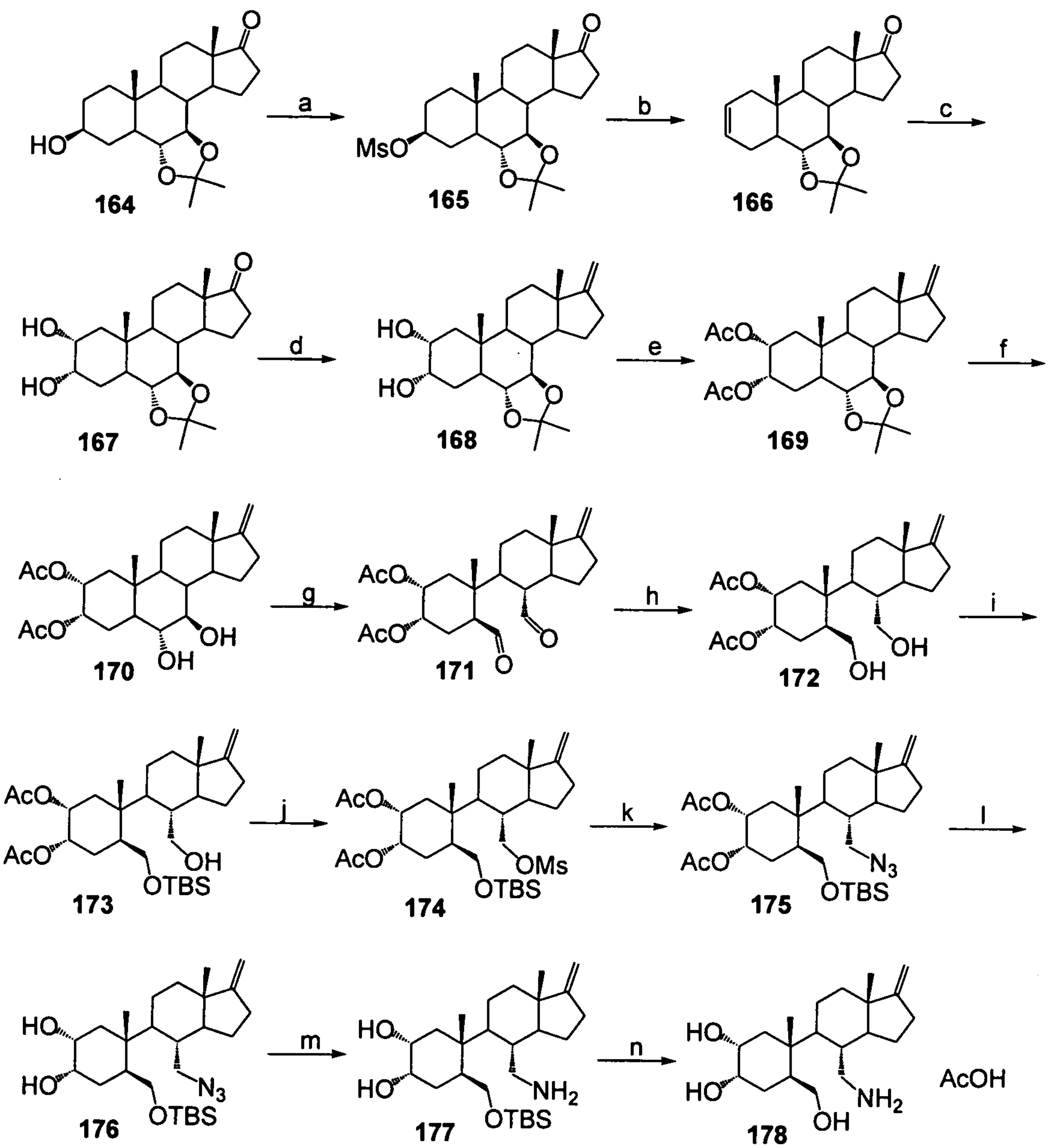
A mixture of compound **162** (0.062 g, 0.11 mmol) and 80% acetic acid (2

mL) was stirred at ambient temperature for 3 hours and then concentrated. The residue was dissolved in toluene and concentrated. The residue was purified by chromatography on silica gel (EtOAc/MeOH, 19:1) to give compound **163** (0.022 g, 65%) as a light yellow solid.

EXAMPLE 17

Compound **178**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 17. Any number of compounds related to compound **178** could be produced using similar methodology. Starting compound **164** may be prepared according to the procedures outlined in U.S. Patent 6,046,185.

REACTION SCHEME 17



a) MsCl, pyridine; b) LiBr, DBU, DMF, 150°C; c) NMO, OsO_4, H_2O, ^tBuOH, THF; d) $MePPh_3Br$, KO^tBu, THF; e) Ac_2O, DMAP, pyridine; f) 80% AcOH; g) $NaIO_4$, H_2O, THF; h) $NaBH_4$, MeOH, THF; i) TBSCl, imidazole, DMF; j) MsCl, pyridine; k) NaN_3, DMF, 40°C; l) K_2CO_3, H_2O, MeOH; m) PPh_3, H_2O, THF, 40°C; n) 80% AcOH.

In general, the free hydroxyl is reacted to give the mesylate compound **165** using MsCl and pyridine. Treatment with LiBr and DBU in DMF gives the elimination product compound **166**. Osmolation gives the compound **167**. Olefination using $MePPh_3Br$ and KO^tBu in THF gives compound **168**. Reaction with acetic

anhydride and DMAP in pyridine gives compound **169**. Treatment with 80% acetic acid removes the acetonide group to give compound **170**. $NaIO_4$ oxidation gives the dialdehyde compound **171**. Sodium borohydride reduction gives compound **172**. Treatment with TBSCl and imidazole in DMF selectively protects one hydroxyl to give compound **173**. The free hydroxyl is reacted to give the mesylate compound **174** using MsCl and pyridine. Azide displacement of the mesylate using sodium azide in DMF gives compound **175**. Base hydrolysis of the acetates gives compound **176**. Reduction of the azide using PPh_3 and water in THF gives compound **177**. Treatment with 80% acetic acid removes the TBS group and forms the salt compound **178**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **165**</u>

To a solution of compound **164** (4.00 g, 11.03 mmol) in pyridine (20 mL) was added MsCl (1.28 mL, 16.55 mmol). The reaction mixture was stirred at ambient temperature for one hour under argon, then diluted with EtOAc (100 mL), washed with brine (2 x 50 mL), dried over anhydrous $MgSO_4$, and concentrated to dryness. The crude product compound **165** used for the next reaction without further purification.

<u>Synthesis of compound **166**</u>

A mixture of crude compound **165** (2.00 g, 4.54 mmol), lithium bromide (0.59 g, 6.81 mmol) and DBU (2 mL, 13.62 mmol) in dry DMF (50 mL) was heated at 150°C for 1.5 hours. After cooling, toluene (120 mL) and water (60 mL) were added to the reaction mixture. The layers were separated and the aqueous phase was extracted with toluene (80 mL). The combined toluene solution was washed with brine (100 mL), dried over anhydrous $MgSO_4$, and concentrated to dryness. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 9/1) to afford impure compound **166** (1.09 g, 70%) as a white solid.

<u>Synthesis of compound **167**</u>

To a solution of compound **166** (1.00 g, 2.90 mmol) in a mixture of THF (15 mL) and *t*-BuOH (5 mL) was added water (2.5 mL), followed by NMO (0.60 mL, 50% in H_2O) and OsO_4 (0.89 mL, 4% in H_2O). The reaction mixture was stirred at ambient

temperature for 3 hours then a solution of $Na_2S_2O_3$ (0.5 g) in water (15 mL) was added. The reaction mixture was stirred for 20 minutes then extracted with CH_2Cl_2 (2 x 30 mL), washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated to dryness. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 1:1) to afford compound **167** (0.65 g, 60%) as a white solid.

<u>Synthesis of compound **168**</u>

A mixture of KO^tBu (2.88 g, 32.9 mmol) and $MePPh_3Br$ (11.8 g, 32.9 mmol) in THF (40 mL) was stirred at ambient temperature for 1 hour then compound **167** (4.15 g, 11.0 mmol) in THF (10 mL) was added and the mixture was stirred at ambient temperature overnight. Saturated $NaHCO_3$ solution (50 mL) was added and the mixture was stirred for 15 minutes, then diluted with water (50 mL) and extracted with EtOAc (4 x 50 mL). The combined organics were washed with brine (2 x 60 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc/MeOH, 1:1:0.02) to give a mixture containing compound **168** (6.29 g) as a light brown foam.

<u>Synthesis of compound **169**</u>

To a solution of the mixture containing compound **168** (6.29 g, 11.0 mmol) and DMAP (0.128 g, 1.05 mmol) in pyridine (40 mL) was added acetic anhydride (4.15 mL, 44.0 mmol). The mixture was stirred at ambient temperature overnight, then diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$ solution (50 mL), water (50 mL) and brine (2 x 50 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 1:3) to give compound **169** (4.12 g, 81% from INT395) as a white foam.

<u>Synthesis of compound **170**</u>

A mixture of compound **169** (1.97 g, 4.28 mmol) and 80% acetic acid (15 mL) was stirred at ambient temperature for 3 hours and then concentrated. The residue was purified by chromatography on silica gel to give compound **170** (1.35 g, 75%) as a yellow foam.

Synthesis of compound **171**

A mixture of compound **170** (1.29 g, 3.07 mmol) and $NaIO_4$ (1.32 g, 6.13 mmol) in THF (20 mL) and water (10 mL) was stirred at ambient temperature. After 1.5 hours, 0.20 g (0.92 mmol) more $NaIO_4$ was added. After 3 hours total reaction time the mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (60 mL). The organic portion was washed with brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated to give crude compound **171** that was used for the next reaction without further purification.

Synthesis of compound **172**

To a solution of crude compound **171** (3.07 mmol) in THF (15 mL) and MeOH (5 mL) at 0°C was added $NaBH_4$ (0.232 g, 6.14 mmol). The mixture was stirred at 0°C for 15 minutes then at ambient temperature for 1.5 hours. The mixture was cooled to 0°C and 80% acetic acid (10 mL) was slowly added. The mixture was stirred at ambient temperature for 10 minutes then diluted with EtOAc (80 mL) and washed with brine (2 x 30 mL). The organic portion was dried over anhydrous $MgSO_4$ and concentrated to give compound **172** (1.23 g, 95% from compound **170**) as a light yellow foam.

Synthesis of compound **173**

A mixture of compound **172** (1.23 g, 2.91 mmol), imidazole (0.600 g, 8.73 mmol) and TBSCl (0.585 g, 3.76 mmol) in DMF (15 mL) was stirred at ambient temperature for 35 minutes, then diluted with water (140 mL) and extracted with Et_2O (4 x 50 mL). The combined organics were washed with brine (2 x 50 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes; hexanes/EtOAc, 9:1, 4:1, 3:1) to give compound **173** (0.992 g, 64%) as a white foam.

Synthesis of compound **174**

To a solution of compound **173** (0.990 g, 1.84 mmol) in pyridine (10 mL) was added methanesulfonyl chloride (0.257 mL, 3.32 mmol). The reaction mixture was

stirred at ambient temperature for 1.5 hours, then diluted with EtOAc (50 mL), washed with water (20 mL) then brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated to afford crude compound **174** (1.17 g, white foam) that was used for the next reaction without further purification.

Synthesis of compound **175**

A mixture of crude compound **174** (1.84 mmol) and NaN_3 (0.242 g, 3.68 mmol) in dry DMF (15 mL) was stirred at 40°C overnight. After cooling to ambient temperature, the mixture was diluted with water (150 mL) and extracted with Et_2O (4 x 50 mL). The combined organics were washed with brine (2 x 50 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes; hexanes/EtOAc, 9:1, 4:1) to give compound **175** (0.708 g, 69% from compound **173**) as a white foam.

Synthesis of compound **176**

A mixture of compound **175** (0.397 g, 0.645 mmol), K_2CO_3 (0.446 g, 3.23 mmol), water (5 mL) and MeOH (15 mL) was stirred at ambient temperature for 4 hours, then diluted with water (100 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed with brine (2 x 50 mL), dried over anhydrous $MgSO_4$ and concentrated to afford compound **176** (0.284 g, 92%) as a white solid that was used for the next reaction without further purification.

Synthesis of compound **177**

A mixture of compound **176** (0.284 g, 0.594 mmol), triphenylphosphine (0.472 g, 1.78 mmol), water (1 mL) and THF (15 mL) was stirred at 40°C overnight and then concentrated. The residue was purified by chromatography on silica gel (CH_2Cl_2; CH_2Cl_2/MeOH, 19:1, 12:1; CH_2Cl_2/MeOH/Et_3N, 9:1:0.3) to give compound **177** (0.241 g, 90%) as a white solid.

Synthesis of compound **178**

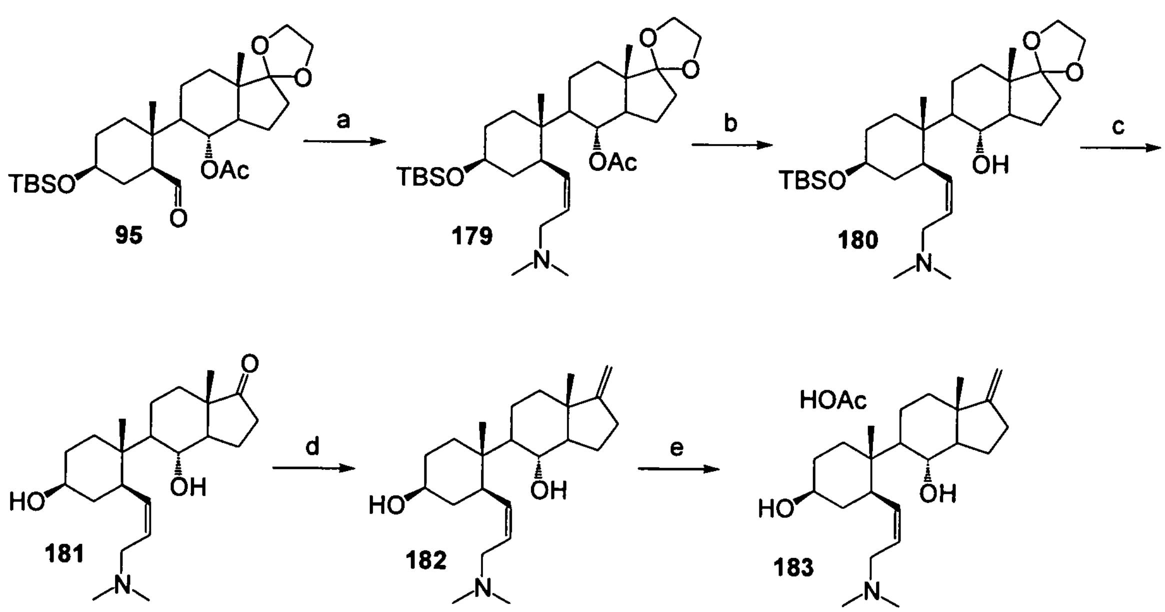
A mixture of compound **177** (0.234 g, 0.518 mmol) and 80% acetic acid (20 mL) was stirred at ambient temperature overnight and then concentrated. The residue was dissolved in MeOH three times and concentrated. Precipitation from

ACN/MeOH (20 mL) gave compound **178** (0.223 g, quantitative) as a white solid. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 338.26; $C_{20}H_{36}NO_3$.

EXAMPLE 18

Compounds **182-185**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 18. Any number of compounds related to compounds **182-185** could be produced using similar methodology. Starting compound **95** may be prepared according to the procedures describe above in Example 10.

REACTION SCHEME 18



a) KO^{t}Bu, $Me_2NCH_2CH_2PPh_3Br$, THF; b) LAH, THF; c) 80% AcOH; d) $MePPh_3Br$, KO^{t}Bu, THF; e) 80% AcOH

In general, olefination using $Me_2NCH_2CH_2PPh_3Br$ and KO^{t}Bu in THF gives compound **179**. Lithium aluminum hydride reduction removes the acyl group to give compound **180**. Treatment with 80% acetic acid removes the cyclic ketal group to give compound **181**. Olefination using $MePPh_3Br$ and KO^{t}Bu in THF gives compound **182**. Treatment with 80% acetic acid forms the salt compound **183**.

Following are specific examples of the compounds prepared above.

Synthesis of compound **179**

A mixture of KO^tBu (101 mg, 0.9 mmol) and (2-dimethylaminoethyl) triphenylphosphonium bromide (373 mg, 0.9 mmol) in THF (10 mL) was stirred at ambient temperature for 1 hour 20 min. A solution of compound **95** (154 mg, 0.3 mmol) in THF (5 mL) was added and the mixture was stirred at ambient temperature overnight. Saturated NH_4Cl (1 mL) was added and the mixture was diluted with EtOAc (100 mL), washed with saturated $NaHCO_3$, brine, dried and concentrated. The crude product was purified by column chromatography (EtOAc/MeOH, 9:1) to give compound **179** (118 mg, 69%).

Synthesis of compound **180**

To a stirred solution of compound **179** (118 mg, 0.21 mmol) in THF (10.5 mL) at 0°C was added 1M LAH in THF (0.63 mL, 0.63 mmol) dropwise. After 30 min at 0°C, the mixture was stirred at ambient temperature for 3 hours. The mixture was cooled to 0°C again and solid $Na_2SO_4.10H_2O$ (203 mg, 0.63 mmol) was added portionwise. After 5 min at 0°C, the mixture was stirred at ambient temperature for 45 min and then filtered through Celite and washed with EtOAc. The filtrate was concentrated, and the crude compound **180** thus obtained was used in next step without purification.

Synthesis of compound **181**

A solution of crude compound **180** obtained above in 80% HOAc (5 mL) was stirred at 40°C for 7 hours 20 min. The solvents were removed by rotary evaporation and the residue was purified by column chromatography (EtOAc/MeOH/water/Et_3N, 7:2:0.5:0.5) to give compound **181** (73 mg, 96% from compound **179**).

Synthesis of compound **182**

A mixture of Ph_3PMeBr (357 mg, 1.0 mmol) and KO^tBu (112 mg, 1.0 mmol) in THF (5 mL) was stirred at ambient temperature for 1 hour 20 min. A solution of compound **181** (73 mg, 0.2 mmol) in THF (3 mL) was added, and the mixture was

stirred at ambient temperature overnight. The reaction was quenched with saturated NH_4Cl (0.5 mL) and the mixture was diluted with EtOAc (150 mL), washed with saturated $NaHCO_3$, brine, dried and concentrated. The residue was purified by column chromatography (EtOAc/MeOH/water/Et_3N, 7:2:0.5:0.5, then EtOAc/MeOH/Et_3N, 7.5:2:0.5) to afford compound **182** (57 mg, 79%).

<u>Synthesis of compound **183**</u>

A solution of compound **182** (57 mg, 0.16 mmol) in 80% HOAc (1 mL) was stirred at 40°C for a few minutes and then the solvents were removed by rotary evaporation and the residue was dried under vacuum. The product was dissolved in a small amount of MeOH and treated with a small amount of ether. The salt precipitated out and dried under vacuum to give compound **183** (68 mg, quant.) as a pale powder. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 362.09; $C_{23}H_{40}NO_2$.

<u>Synthesis of compound **184**</u>

Using the procedures described for the synthesis of compound **183**, with the exception of olefination by (4-chlorobenzyl)triphenyl-phosphonium chloride, compound **184** (34 mg) was prepared in 51% yield starting from compound **95**. Other notable exceptions were the use of HCl in MeOH to affect the desilylation/deketalization step (to prepare the intermediate analogous to compound **181**) and the inclusion of the following double bond hydrogenation step. The intermediate analogous to compound **181** was treated with a catalytic amount of 10% Pd on carbon in THF and MeOH while under H_2 atmosphere. The catalyst was filtered off and the filtrate was concentrated. The crude intermediate was treated with 80% HOAc to form the acetate salt of compound **184**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 434.68; $C_{26}H_{41}ClNO_2$.

<u>Synthesis of compound **185**</u>

Step 1: Synthesis of (3-pyridylmethyl)triphenylphosphonium chloride

To a stirred solution of 3-(chloromethyl)pyridine hydrochloride (5.17 g, 31.5 mmol) in water (8 mL) was added K_2CO_3 (4.34 g, 31.5 mmol) portionwise. The

resulting mixture was extracted three times with diethyl ether. The extracts were combined and washed twice with brine, dried and concentrated. The residue (3.25 g, 25.5 mmol) was dissolved in xylene (30 mL) and Ph_3P (6.70 g, 25.5 mmol) was added. The mixture was heated at 133-134°C overnight and then cooled to ambient temperature. The solid product was filtered, washed with toluene, and dried under vacuum to give (3-pyridylmethyl)triphenylphosphonium chloride (5.86 g, 48%) as a pinkish solid.

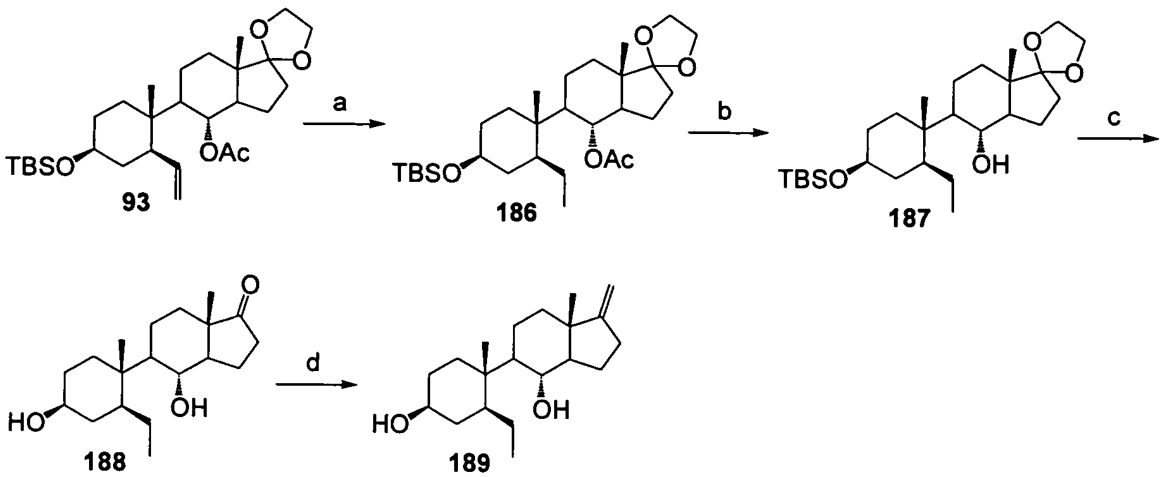
Step 2: Synthesis of compound **185**

Using the procedures described above for the synthesis of compound **184**, with the exception of substitution by (3-pyridylmethyl)triphenylphosphonium chloride, compound **185** (19 mg) was prepared in 20% yield starting from compound **95**. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 384.15; $C_{25}H_{38}NO_2$.

EXAMPLE 19

Compound **189**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 19. Any number of compounds related to compound **189** could be produced using similar methodology. Starting compound **93** may be prepared according to the procedures described above in Example 10.

REACTION SCHEME 19



a) H_2, 10% Pd/C; b) LAH, THF; c) 80% AcOH; d) $MePPh_3Br$, KO^tBu, THF

In general, catalytic hydrogenation of the double bond gives compound **186**. Lithium aluminum hydride reduction removes the acyl group to give compound **187**. Treatment with 80% acetic acid removes both the TBS group and the cyclic ketal group to give compound **188**. Olefination using $MePPh_3Br$ and KO^tBu in THF gives compound **189**.

Following are specific examples of the compounds prepared above.

Synthesis of compound **186**

A mixture of compound **93** (98 mg, 0.19 mmol), 10% Pd/C (10 mg) in EtOH (4 mL) was stirred under H_2 (1 atm) overnight. The catalyst was removed by filtration and the filtrate was concentrated. The crude compound **186** (98 mg) was used in next step without purification.

Synthesis of compound **187**

To a stirred solution of compound **186** (98 mg, 0.19 mmol) in THF (9 mL) at 0°C was added 1M LAH in THF (0.86 mL, 0.86 mmol) dropwise. After 5 min at 0°C, the mixture was stirred at ambient temperature for 6 hours. The mixture was cooled to 0°C again and solid $Na_2SO_4.10H_2O$ (275 mg, 0.86 mmol) was added portionwise. After 5 min at 0°C, the mixture was stirred at ambient temperature for 1 hour and then filtered

through Celite. The filtrate was concentrated, and the crude product was purified by column chromatography (hexanes/EtOAc, 1:1) to give compound **187**.

Synthesis of compound **188**

A solution of compound **187** obtained above in 80% HOAc (5 mL) was stirred at 40°C for 7.5 hours. The solvents were removed by rotary evaporation and the residue was purified by column chromatography (EtOAc/hexanes, 8:2 then 9:1) to give compound **188** (35 mg, 59% from compound **186**).

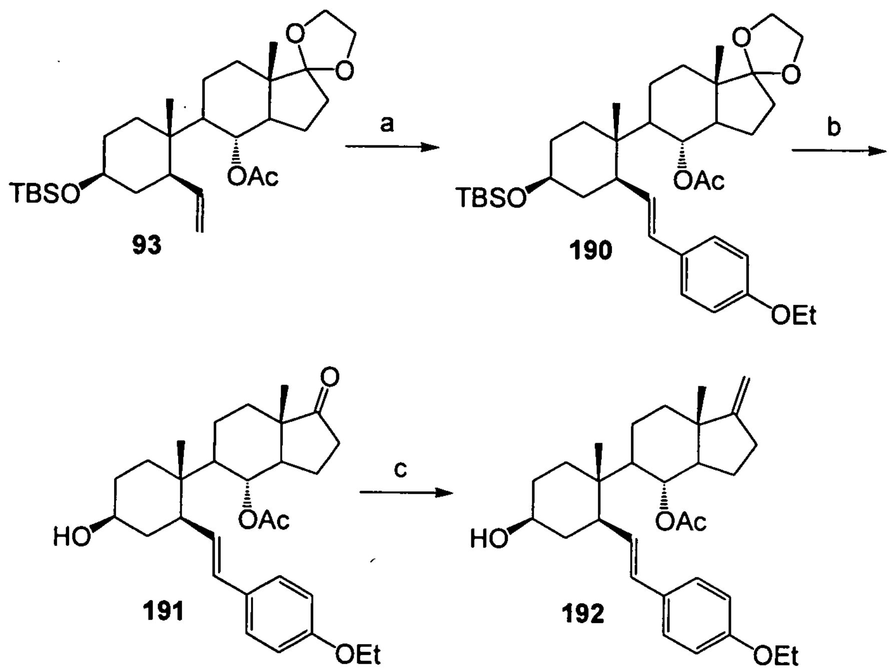
Synthesis of compound **189**

A mixture of Ph_3PMeBr (196 mg, 0.55 mmol) and KO^tBu (62 mg, 0.54 mmol) in THF (5 mL) was stirred at ambient temperature for 1.5 hours. A solution of compound **188** (35 mg, 0.11 mmol) in THF (2 mL) was added, and the mixture was stirred at ambient temperature overnight. The reaction was quenched with saturated NH_4Cl (1 mL) and the mixture was diluted with EtOAc (150 mL), washed with brine, dried and concentrated. The residue was purified by column chromatography (EtOAc/hexanes, 7:3) to yield compound **189** (37 mg, quant.). LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 324.74; $C_{20}H_{38}NO_2$.

EXAMPLE 20

Compound **192**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 20. Any number of compounds related to compound **192** could be produced using similar methodology.

REACTION SCHEME 20



a) 4-BrC_6H_4OEt, P(o-tol)$_3$, Pd(OAc)$_2$, Et_3N; b) 80% AcOH; c) Ph_3PMeBr, KO^{t}Bu, THF

In general, palladium catalyzed coupling of the olefin **93** with the aryl halide 4-BrC_6H_4OEt gives compound **190**. Treatment with 80% acetic acid removes the TBS group and the cyclic ketal to give compound **191**. Olefination using $MePPh_3Br$ and KO^{t}Bu in THF gives compound **192**.

Following are specific examples of the compounds prepared above.

Synthesis of compound **190**

A mixture of compound **93** (100 mg, 0.2 mmol), 4-bromophenetole (0.04 mL, 0.28 mmol), tri(orthotolyl)phosphine (12 mg, 0.04 mmol), Pd(OAc)$_2$ (2.3 mg, 0.01 mmol), Et_3N (0.06 mL) in acetonitrile (2 mL) was heated at 80°C overnight. The solvents were removed and the residue was purified by column chromatography (hexanes/EtOAc, 9:1 then 85:15) to yield compound **190** (61 mg, 49%).

Synthesis of compound **191**

A solution of compound **190** in 80% HOAc (5 mL) was stirred at 40°C for 7.5 hours. The solvents were removed by rotary evaporation and the residue was

purified by column chromatography (EtOAc/hexanes, 8:2) to give compound **191** (27 mg, 60%).

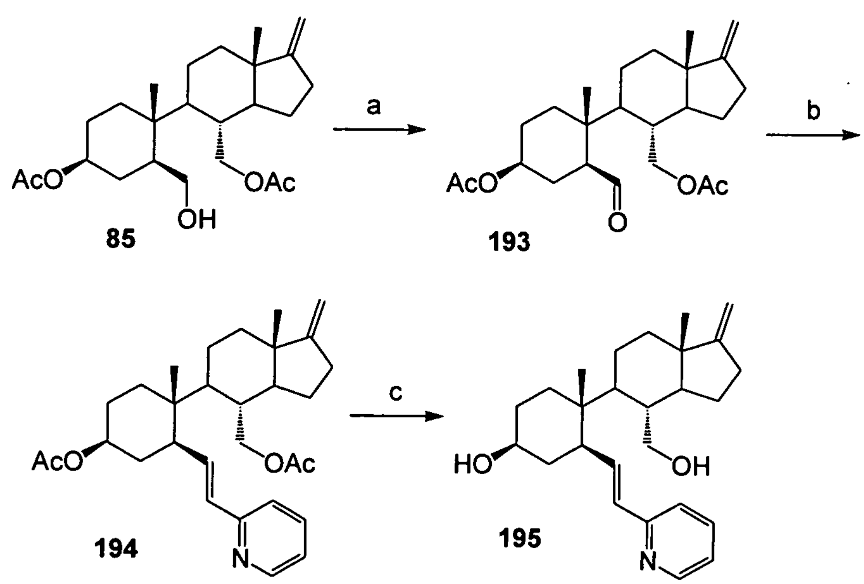
Synthesis of compound **192**

A mixture of Ph_3PMeBr (114 mg, 0.32 mmol) and KO^tBu (36 mg, 0.32 mmol) in THF (3 mL) was stirred at ambient temperature for 1.5 hours. A solution of compound **191** (27 mg, 0.064 mmol) in THF (1 mL) was added, and the mixture was stirred at ambient temperature overnight. The reaction was quenched with saturated NH_4Cl (1 mL) and the mixture was diluted with EtOAc (150 mL), washed with brine, dried and concentrated. The residue was purified by column chromatography (EtOAc/hexanes, 1:1) to yield compound **192** (13 mg, 43%). LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 484.69; $C_{30}H_{46}NO_4$.

EXAMPLE 21

Compounds **195-201**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 21. Any number of compounds related to compounds **195-201** could be produced using similar methodology. Starting compound **85** may be prepared according to procedures described above in Example 9.

REACTION SCHEME 21



a) TPAP, NMO, CH_2Cl_2; b) KO^{t}Bu, (2-pyridylmethyl)triphenylphosphonium chloride, THF; c) LAH, THF.

In general, TPAP catalyzed oxidation of the free alcohol gives compound **193**. Olefination using (2-pyridylmethyl)triphenylphosphonium chloride and KO^{t}Bu in THF gives compound **194**. Lithium aluminum hydride reduction removes the acyl groups to give compound **195**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **193**</u>

To a solution of compound **85** (11.6 g, 28.4 mmol) in CH_2Cl_2 (100 mL) at 0°C were added TPAP (1.50 g, 4.26 mmol) and NMO (9.98 g, 85.2 mmol). The mixture was stirred at 0°C for 10 minutes then at ambient temperature for 3 hours. The mixture was concentrated to dryness and the residue was purified by chromatography on silica gel (hexanes/EtOAc, 3:2, 1:1; EtOAc) to give compound **193** (8.61 g, 75%) as a white solid.

<u>Synthesis of compound **194**</u>

Step 1: Synthesis of (2-pyridylmethyl)triphenylphosphonium chloride)

To a stirred solution of 2-(chloromethyl)pyridine hydrochloride (8.0 g, 48.8 mmol) in water (20 mL) was added K_2CO_3 (6.74 g, 48.7 mmol) portionwise. The resulting mixture was extracted four times with diethyl ether. The extracts were combined and washed twice with brine, dried and concentrated. The residue (5.78 g, 45.3 mmol) was dissolved in 1,4-dioxane (19 mL) and Ph_3P (11.89 g, 45.3 mmol) was added. The mixture was heated at 110°C overnight and then cooled to ambient temperature. The solid product was filtered, washed with ether, and dried under vacuum to give (2-pyridylmethyl)triphenylphosphonium chloride (15.78 g, 83%) as a pale solid.

Step 2: Synthesis of compound **194**

A mixture of KO^{t}Bu (132 mg, 1.2 mmol) and (2-pyridylmethyl) triphenylphosphonium chloride (460 mg, 1.2 mmol) in THF (15 mL) was stirred at

ambient temperature for 1.5 hours. A solution of compound **193** (195 mg, 0.48 mmol) in THF (5 mL) was added and the mixture was stirred at ambient temperature overnight. Saturated NH_4Cl (1 mL) was added and the mixture was diluted with EtOAc (150 mL), washed with brine, dried and concentrated. The crude product was purified by column chromatography (EtOAc/hexanes, 1:1) to give compound **194** (207 mg, 90%).

Synthesis of compound **195**

To a stirred solution of compound **194** (207 mg, 0.43 mmol) in THF (15 mL) at 0°C was added 1M LAH in THF (1.9 mL, 1.9 mmol) dropwise. After 5 min at 0°C, the mixture was stirred at ambient temperature for 6 hours. The reaction was cooled to 0°C again and solid $Na_2SO_4.10H_2O$ (623 mg, 1.9 mmol) was added portionwise. After 5 min at 0°C, the mixture was stirred at ambient temperature for 1 hour and then filtered through Celite and washed with EtOAc. The filtrate and washings were combined and concentrated. The residue was purified by column chromatography (EtOAc/MeOH, 95:5) to yield compound **195** (135 mg, 79%): LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 396.43; $C_{26}H_{38}NO_2$.

Synthesis of compound **196**

Using the procedures described for the synthesis of compound **195**, with the exception of olefination by (3-pyridylmethyl)triphenylphosphonium chloride, compound **196** (90 mg) was prepared in 61% yield starting from compound **193**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 396.17; $C_{26}H_{38}NO_2$.

Synthesis of compound **197**

Using the procedures described for the synthesis of compound **195**, with the exception of olefination by hexyltriphenylphosphonium bromide, compound **197** (*Z*-isomer, 124 mg) was prepared in 85% yield starting from compound **193**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 405.86; $C_{26}H_{48}NO_2$.

Synthesis of compounds **198** and **201**

Using the procedures described for the synthesis of compound **195**, with the exception of olefination by (3-benzyloxypropyl)triphenylphosphonium bromide,

compound **198** (*Z*-isomer, 114 mg, 68%) and compound **201**, product of debenzylation, (*Z*-isomer, 10 mg, 7%) were prepared starting from compound **193**. Compound **198**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 452.57; $C_{30}H_{44}O_3$. Compound **201**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 363.15; $C_{23}H_{39}O_3$.

<u>Synthesis of compound **199**</u>

Using the procedures described for the synthesis of compound **195**, with the exceptions of olefination by (2-dimethylaminoethyl)triphenylphosphonium bromide, and salt formation with acetic acid, compound **199** (*Z*-isomer, 93 mg) was prepared in 57% yield starting from compound **193**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 376.06; $C_{24}H_{42}NO_2$.

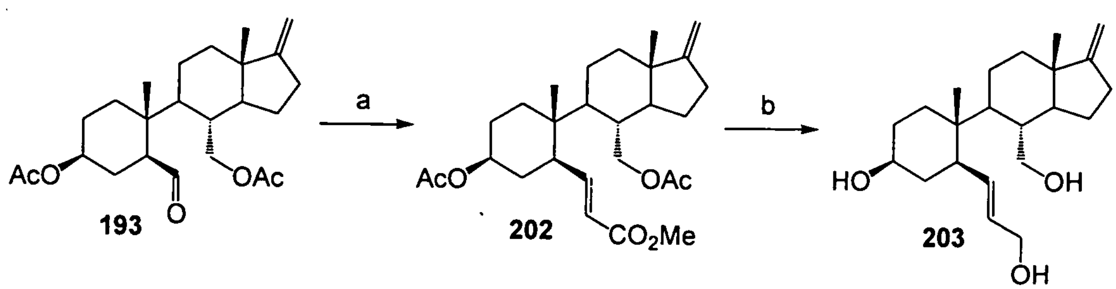
<u>Synthesis of compound **200**</u>

Using the procedures described for the synthesis of compound **195**, with the exceptions of olefination by (4-chlorobenzyl)triphenylphosphonium chloride, compound **200** (118 mg) was prepared in 74% yield starting from compound **193**.

EXAMPLE 22

Compound **203**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 22. Any number of compounds related to compound **203** could be produced using similar methodology. Starting compound **193** may be prepared according to procedures described above in Example 21.

REACTION SCHEME 22



a) Ph_3PCHCO_2Me, THF; b) LAH, THF

In general, olefination using methyl (triphenylphosphoranylidene)acetate in THF gives compound **202**. Lithium aluminum hydride reduces the ester groups to give compound **203**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **202**</u>

A mixture of compound **193** (300 mg, 0.74 mmol) and methyl (triphenylphosphoranylidene)acetate (742 mg, 2.2 mmol) in THF (30 mL) was stirred at 67°C overnight and then at 80°C for one day. The solvent was removed and the residue was purified by column chromatography (hexanes /EtOAc, 8:2) to give compound **202** (328 mg, 96%).

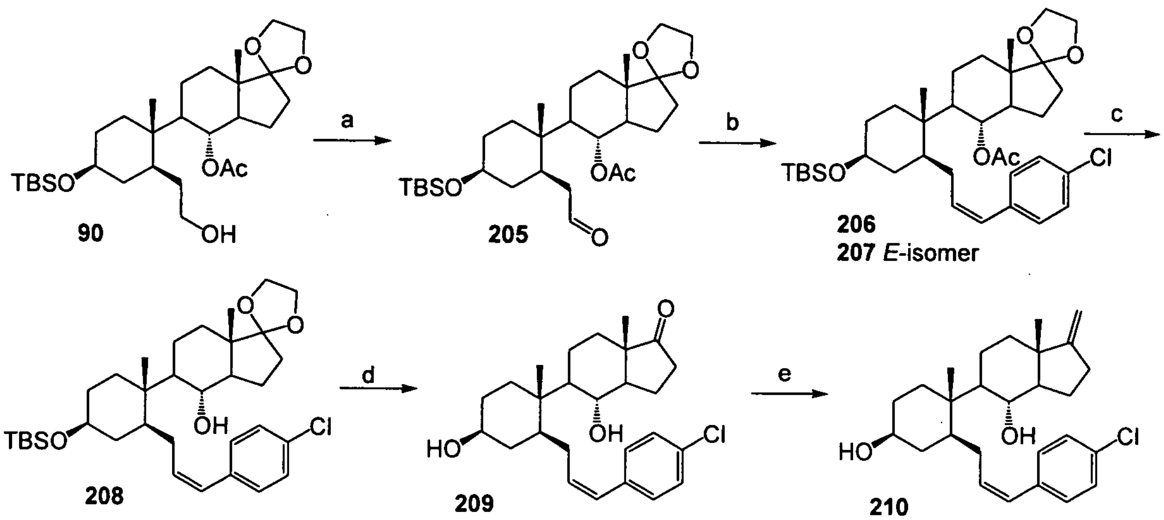
<u>Synthesis of compound **203**</u>

To a stirred solution of compound **202** (179 mg, 0.39 mmol) in THF (15 mL) at 0°C was added 1M LAH in THF (2.2 mL, 2.2 mmol) dropwise. After 5 min at 0°C, the mixture was stirred at ambient temperature for 6 hours 10 min. The reaction was cooled to 0°C again and solid $Na_2SO_4.10H_2O$ (715 mg, 2.2 mmol) was added portionwise. After 5 min at 0°C, the mixture was stirred at ambient temperature for 1 hour and then filtered through Celite and washed with EtOAc. The filtrate and washings were combined and concentrated. The residue was purified by column chromatography (EtOAc/MeOH, 95:5) to yield compound **203** (66 mg, 49%): LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 331.06; $C_{22}H_{35}O_2$.

EXAMPLE 23

Compounds **210-212** may be prepared according to the following Reaction Scheme 23. Any number of compounds related to compounds **210-212** could be produced using similar methodology. Starting compound **90** may be prepared according to procedures described above in Example 10.

REACTION SCHEME 23



a) NMO, TPAP, CH_2Cl_2; b) (4-chlorobenzyl)triphenylphosphonium chloride, KO^tBu, THF; c) $LiAlH_4$, THF; d) 80% AcOH, MeOH, THF, 40°C; e) $MePPh_3Br$, KO^tBu, THF.

In general, TPAP catalyzed oxidation of the free alcohol gives compound **205**. Olefination using (4-chlorobenzyl)triphenylphosphonium chloride and KO^tBu in THF gives compound **206** and the *E*-isomer compound **207**. Lithium aluminum hydride reduction removes the acyl group to give compound **208**. Treatment with 80% acetic acid removes the TBS group and the cyclic ketal group to give compound **209**. Olefination using $MePPh_3Br$ and KO^tBu in THF gives compound **210**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **205**</u>

To a solution of compound **204** (8.60 g, 16.4 mmol) in CH_2Cl_2 (100 mL) at 0°C were added TPAP (0.86 g, 2.5 mmol) and NMO (5.76 g, 49.2 mmol). The mixture was stirred at 0°C for 5 minutes then at ambient temperature. After 3 hours, more TPAP (0.29 g, 0.83 mmol) and NMO (1.92 g, 16.4 mmol) were added and stirring continued. After 5.5 hours total reaction time the mixture was concentrated to dryness. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 49:1, 19:1, 9:1, 4:1) to give compound **205** (5.13 g, 60%) as a white solid.

anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 3:1, 1:1) to afford compound **210** (0.035 g, 21% from compound **205**) as a white solid after concentration from CH_2Cl_2. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 411.14; $C_{27}H_{36}ClO$.

<u>Synthesis of compound **211**</u>

Using the procedure described for the synthesis of compound **208**, compound **207** (0.126 g, 0.200 mmol) was reacted with $LiAlH_4$ (0.80 mL of a 1 M solution in THF, 0.80 mmol) to give the alcohol intermediate (0.121 g, colourless glass). Using the procedure described for the synthesis of compound **209**, the alcohol intermediate (0.20 mmol) was converted to ketone intermediate (0.104 g, colourless glass). Using the procedure described for the synthesis of compound **210**, with the exception that a different solvent system was used for chromatography on silica gel (hexanes/EtOAc, 4:1, 7:3, 3:2, 1:1), the ketone intermediate (0.20 mmol) was converted to the alkene. Concentration from CH_2Cl_2 gave compound **211** (0.058 g, 36% from compound **205**) as a light yellow solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 411.09; $C_{27}H_{36}ClO$.

<u>Synthesis of compound **212**</u>

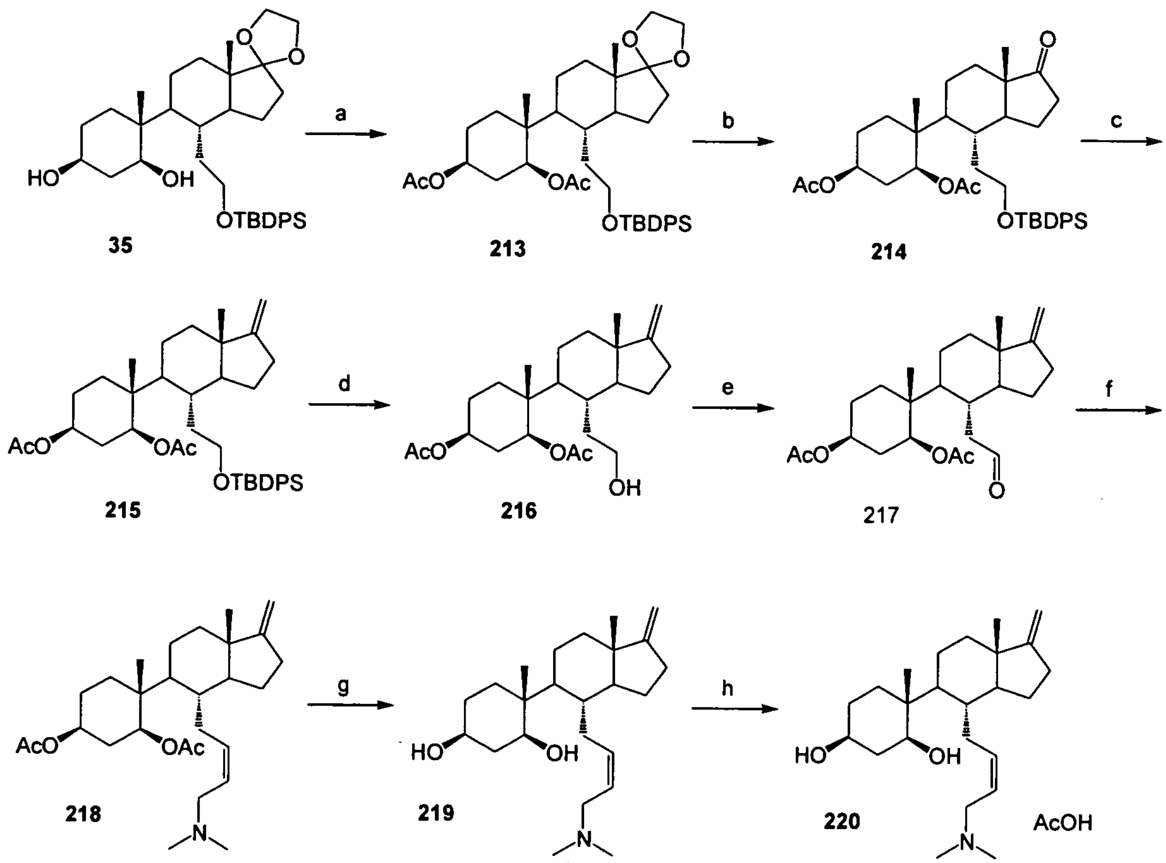
Using the procedure described for the synthesis of compound **206**, with the exception that a different solvent system was used for chromatography on silica gel (EtOAc/MeOH, 9:1; EtOAc/MeOH/Et_3N, 9:0.75:0.25), compound **205** (0.20 g, 0.38 mmol) was reacted with (2-dimethylaminoethyl)triphenylphosphonium bromide (0.485 g, 1.15 mmol) to give the amine intermediate (0.204 g, 93%, yellow oil). Using the procedure described for the synthesis of compound **208**, with the exceptions that 0.76 mL more $LiAlH_4$ solution (1 M in THF, 0.76 mmol) were added after 2.5 hours and total reaction time was 5.5 hours, the amine intermediate (0.35 mmol) was reacted with $LiAlH_4$ (0.76 mL of a 1 M solution in THF, 0.76 mmol) to give the alcohol intermediate (0.203 g, colourless glass). Using the procedure described for the synthesis of compound **209**, with the exceptions that THF and MeOH were not added and the reaction mixture was not heated, the alcohol intermediate (0.35 mmol) was converted to

ketone intermediate as the acetic acid salt (0.189 g, colourless glass). Using the procedure described for the synthesis of compound **210**, with the exceptions that 0.331 g (2.80 mmol) KO^tBu, 1.00 g (2.80 mmol) $MePPh_3Br$ and 15 mL THF were used, and after quenching the reaction mixture was concentrated, then purified by chromatography on silica gel (EtOAc/MeOH, 9:1; EtOAc/MeOH/Et_3N, 9:0.9:0.1, 9:0.75:0.25), the ketone intermediate (0.35 mmol) was converted to the alkene. A mixture of the alkene, 80% AcOH (1 mL) and MeOH (5 mL) was concentrated by rotary evaporation. Precipitation from Et_2O afforded compound **212** (0.072 g, 43% from compound **205**) as a white solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 375.98; $C_{24}H_{42}NO_2$.

EXAMPLE 24

Compounds **219-222**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 24. Any number of compounds related to compounds **219-222** could be produced using similar methodology. Starting compound **35** may be prepared according to procedures described above in Example 3.

REACTION SCHEME 24



a) Ac_2O, DMAP, pyridine; b) HCl, H_2O, THF, 60-65°C; c) $MePPh_3Br$, KO^tBu, THF; d) TBAF, THF, 70°C; e) NMO, TPAP, CH_2Cl_2; f) (2-dimethylaminoethyl)triphenylphosphonium bromide, KO^tBu, THF; g) $LiAlH_4$, THF; h) 80% AcOH, MeOH.

In general, reaction with acetic anhydride and DMAP in pyridine gives compound **213**. Treatment with HCl and water in THF removes the cyclic ketal group to give compound **214**. Olefination using $MePPh_3Br$ and KO^tBu in THF gives compound **215**. Tetrabutylammonium fluoride removes the *tert*-butyldiphenylsilyl group to give compound **216**. TPAP catalyzed oxidation of the free alcohol gives compound **217**. Olefination using (2-dimethylaminoethyl)triphenylphosphonium bromide and KO^tBu in THF gives compound **218**. Lithium aluminum hydride reduction removes the acyl groups to give compound **219**. Treatment with 80% acetic acid forms the salt compound **220**.

Following are specific examples of the compounds prepared above.

Synthesis of compound **213**

To a solution of compound **35** (67 mmol) in pyridine (150 mL) at 0°C were added DMAP (1.0 g, 8.2 mmol) and acetic anhydride (12.7 mL, 134 mmol). The reaction mixture was stirred at ambient temperature for 2 hours. The reaction was quenched with water and diluted with EtOAc, then concentrated to dryness to give crude compound **213** that was used for the next reaction without further purification.

Synthesis of compound **214**

A mixture of compound **213** (67 mmol), HCl (20 mL), water (50 mL) and THF (150 mL) was stirred at 60 - 65°C for 2 hours, then cooled to ambient temperature. With K_2CO_3 the mixture was adjusted to pH = 7.0 – 8.0, then water and CH_2Cl_2 were added. The mixture was dried over anhydrous $MgSO_4$ and concentrated. Precipitation from EtOAc gave a crude mixture that contained compound **214** (white solid) and was used in the next reaction without further purification.

Synthesis of compound **215**

A mixture of KO^tBu (9.43 g, 83.9 mmol) and $MePPh_3Br$ (30.0 g, 83.9 mmol) in THF (200 mL) was stirred at ambient temperature, then crude compound **214** (67 mmol) was added and the mixture was stirred at ambient temperature for 2 hours. The reaction was quenched with cold water and extracted with EtOAc. The organic portion was concentrated to dryness, then the residue was treated with hexanes/EtOAc (4:1), filtered and the filtrate was concentrated to dryness. The residue was dissolved in pyridine and acetic anhydride was added. The mixture was stirred at ambient temperature for 2 hours, then quenched with water and extracted with EtOAc. The organic portion was concentrated to dryness to give crude compound **215** that was used in the next reaction without further purification.

Synthesis of compound **216**

A mixture of crude compound **215** (67 mmol) and TBAF (30 mL of a 1 M solution in THF, 30 mmol) in THF (80 mL) was stirred at ambient temperature for 2 hours then at 70°C for 1 hour. The mixture was concentrated and the residue was purified by chromatography on silica gel to give compound **216** (6.12 g, 22% from

compound **35**) as a white solid.

Synthesis of compound **217**

To a solution of compound **216** (6.0 g, 15 mmol) in CH_2Cl_2 (50 mL) were added TPAP (0.052 g, 0.15 mmol) and NMO (4.4 g, 38 mmol). The mixture was stirred at ambient temperature. After 2 hours, more TPAP (0.052 g, 0.15 mmol) was added and stirring continued. After 3 hours total reaction time, the mixture was concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 9:1) to give compound **217** (2.9 g, 48%) as a white solid.

Synthesis of compound **218**

A mixture of KO^tBu (0.157, 1.33 mmol) and (2-dimethylaminoethyl)triphenylphosphonium bromide (0.563 g, 1.33 mmol) in THF (10 mL) was stirred at ambient temperature for 1 hour, then a solution of compound **217** (0.20 g, 0.49 mmol) in THF (5 mL) was added. The reaction mixture was stirred at ambient temperature overnight, then quenched with saturated NH_4Cl solution (1 mL), diluted with EtOAc (150 mL), washed with brine (2 x 25 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (EtOAc/MeOH, 9:1; EtOAc/MeOH/Et_3N, 9:0.75:0.25) to give compound **218** (0.197, 88%) as a white foam.

Synthesis of compound **219**

To a solution of compound **218** (0.197 g, 0.428 mmol) in THF (10 mL) was added $LiAlH_4$ (0.98 mL of a 1 M solution in THF, 0.98 mmol). The mixture was stirred at ambient temperature for 4 hours, then quenched with $Na_2SO_4 \cdot 10H_2O$ and stirred for 30 minutes. The mixture was filtered, rinsing with EtOAc, and concentrated to dryness. The residue was purified by chromatography on silica gel (EtOAc/MeOH, 9:1; EtOAc/MeOH/Et_3N, 9:0.75:0.25, 9:0.5:0.5) to give compound **219** as a white solid that was used for the next reaction.

Synthesis of compound **220**

A mixture of compound **219**, 80% AcOH (1 mL) and MeOH (5 mL) was concentrated by rotary evaporation. Concentration from CH_2Cl_2 afforded compound

220 (0.154 g, 72% from compound **217**) as a white foam: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 375.96; $C_{24}H_{42}NO_2$.

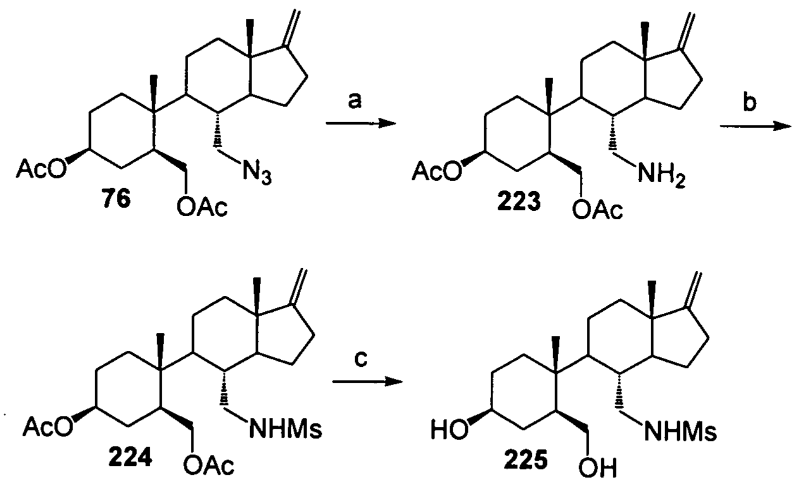
<u>Synthesis of compounds **221** and **222**</u>

Using the procedure described for the synthesis of compound **218**, with the exception that a different solvent system was used for chromatography on silica gel (hexanes/EtOAc, 3:1, 3:2), compound **217** (0.20 g, 0.49 mmol) was reacted with (3-pyridylmethyl)triphenylphosphonium chloride (0.519 g, 1.33 mmol) to give a mixture of alkene intermediates (0.195 g, colourless glass). Using the procedure described for the synthesis of compound **219**, with the exceptions that reaction time was 3 hours and different solvent systems were used for chromatography on silica gel (EtOAc/MeOH and CH_2Cl_2/acetone), the alkene intermediate mixture (0.41 mmol) was reacted with $LiAlH_4$ (0.81 mL of a 1 M solution in THF, 0.81 mmol) to give compound **221** (*Z*-isomer) (0.037 g, 19% from compound **217**) as a white foam after concentration from CH_2Cl_2 and compound **222** (*E*-isomer) (0.047 g, 24% from compound **217**) as a white solid after precipitation from Et_2O. Compound **221**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 395.98; $C_{26}H_{38}NO_2$. Compound **222**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 395.96; $C_{26}H_{38}NO_2$.

EXAMPLE 25

Compound **225**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 25. Any number of compounds related to compound **225** could be produced using similar methodology. Starting compound **76** may be prepared according to procedures described above in Reaction Scheme 8.

REACTION SCHEME 25



a) PPh_3, THF, H_2O; b) MsCl, Et_3N, CH_2Cl_2; c) K_2CO_3, MeOH, H_2O.

In general, reaction of compound **76** with triphenylphosphine and water in THF reduces the azide group to give compound **223**. The amine group is converted to the sulfonamide compound **224** using MsCl and triethylamine in CH_2Cl_2. Treatment with potassium carbonate in methanol and water gives compound **225**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **223**</u>

A solution of compound **76** (6.00 g, 13.9 mmol), PPh_3 (5.85 g, 22.3 mmol), water (3.72 mL, 206 mmol) and THF (100 mL) was heated overnight at 40°C. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel (EtOAc/MeOH/Et_3N 90:10 then 90:10:3) to afford compound **223** (4.59 g, 81%) as a white foam.

<u>Synthesis of compound **224**</u>

A solution of compound **223** (250 mg, 0.616 mmol), MsCl (72 μL, 0.92 mmol), Et_3N (258 μL, 1.84 mmol) and CH_2Cl_2 was stirred at ambient temperature under argon for 1.5 hours. The reaction was quenched with saturated $NaHCO_3$ solution (3 mL) and water (2 mL). The solution was further diluted with water (5 mL) and was extracted with 100 mL of EtOAc. The EtOAc solution was washed with water and brine,

then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc 3:1, then 1:1) to afford compound **224** (310 mg, quantitative) as a white foam.

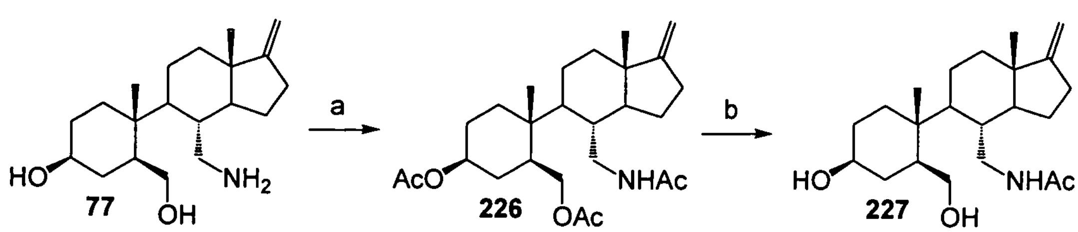
Synthesis of compound **225**

A solution of compound **224** (223 mg, 0.46 mmol), K_2CO_3 (255 mg, 1.84 mmol), water (3 mL) and methanol (6 mL) was heated at reflux for 2 hours. The reaction mixture was concentrated, then dissolved in water and CH_2Cl_2 and was extracted with CH_2Cl_2 (240 mL). The CH_2Cl_2 solution was washed with water and brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 100:0, then 19:1, then 9:1). The residue from the pure fractions was concentrated from a minimum of MeOH and acetonitrile (5 mL) to afford compound **225** (132 mg, 72%) as a white powder: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 381.90; $C_{21}H_{35}NO_3S$, 363.85; $C_{21}H_{33}NO_2S$.

EXAMPLE 26

Compound **227**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 26. Any number of compounds related to compound **227** could be produced using similar methodology. Starting compound **77** may be prepared according to procedures described above in Example 8.

REACTION SCHEME 26



a) Ac_2O, DMAP, pyridine; b) $LiAlH_4$, THF.

In general, reaction of compound **77** with acetic anhydride and DMAP in

pyridine acylates the hydroxyl and amino groups to give compound **226**. Selective lithium aluminum hydride reduction of the acetates gives compound **227**.

Following are specific examples of the compounds prepared above.

Synthesis of compound **226**

A solution of compound **77** (208 mg, 0.647 mmol), acetic anhydride (214 µL, 2.27 mmol), DMAP (17 mg) and pyridine (5 mL) was stirred overnight at ambient temperature. The reaction was quenched with brine and was extracted with EtOAc. The EtOAc solution was washed with brine, then dried over $MgSO_4$, filtered and concentrated. The residual solvent was removed by codistillation with toluene. The residue was purified by chromatography on silica gel (EtOAc) to afford compound **226** (235 mg, 81%).

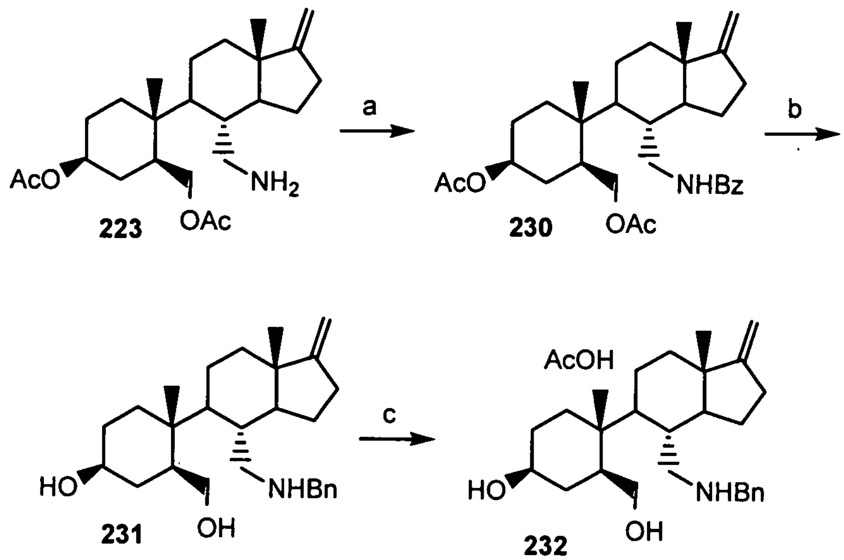
Synthesis of compound **227**

A solution of $LiAlH_4$ (1.57 mL of a 1.0 M solution in THF) was added to an ice cooled solution of compound **226** (235 mg, 0.525 mmol) in THF (10 mL). After 10 minutes the solution was continued at ambient temperature for another 2 hours. The reaction was quenched with $Na_2SO_4 \cdot 10H_2O$. After 1 hour $MgSO_4$ was added and the solution was filtered and concentrated. The resulting crystalline solid was triturated successively with Et_2O, CH_2Cl_2, EtOAc and MeOH to afford compound **227** (128 mg, 67%) as a white powder. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 386.48; $C_{22}H_{37}NNaO_3$.

EXAMPLE 27

Compounds **229** and **231-233**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 27. Any number of compounds related to compounds **229** and **231-233** could be produced using similar methodology. Starting compound **223** may be prepared according to procedures described above in Example 25.

REACTION SCHEME 27



a) BzCl, DMAP, pyridine, CH_2Cl_2, pyridine; b) $LiAlH_4$, THF; c) 80% AcOH.

In general, reaction of an amino compound such as compound **223** with benzoyl chloride gives the amide compound **230**. Lithium aluminum hydride reduces the amide and the acetates to give compound **231**. Treatment with 80% acetic acid forms the salt compound **232**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **230**</u>

A solution of compound **223** (405 mg, 1.00 mmol), benzoyl chloride (0.17 mL, 1.46 mmol), DMAP (15 mg), pyridine (4 mL) and CH_2Cl_2 (6 mL) was stirred for 2 hours at ambient temperature. The reaction was diluted with EtOAc (250 mL) and was washed with saturated $NaHCO_3$ solution and brine, then dried over $NaSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexanes 45:55) to afford compound **230** (490 mg, 96%) as a colourless syrup.

<u>Synthesis of compound **231**</u>

A solution of $LiAlH_4$ (6 x 4.8 mL of a 1.0 M solution in THF) was added over 3 days to a solution of compound **230** (490 mg, 0.96 mmol) in THF (20 mL) at reflux under argon. The reaction was cooled in ice and was quenched with

$Na_2SO_4 \cdot 10H_2O$. After 20 minutes the solution was filtered and concentrated. The residue was purified by chromatography (EtOAc/MeOH 95:5) to afford compound **231** (395 mg, 39%) as a crystalline solid.

Synthesis of compound **232**

A solution of compound **231** (150 mg, 0.36 mmol) and 80% AcOH was heated at 40°C for 10 minutes. The solution was concentrated to give compound **232** (162 mg, 94%) as a white foam. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 412.16; $C_{27}H_{42}NO_2$.

Synthesis of compound **233**

Using the procedures described for the synthesis of compound **232**, with the exception of substitution by cyclopropane carbonyl chloride, compound **233** (231 mg) was prepared as a white solid in 67% yield starting from compound **223**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 376.35; $C_{24}H_{42}NO_2$.

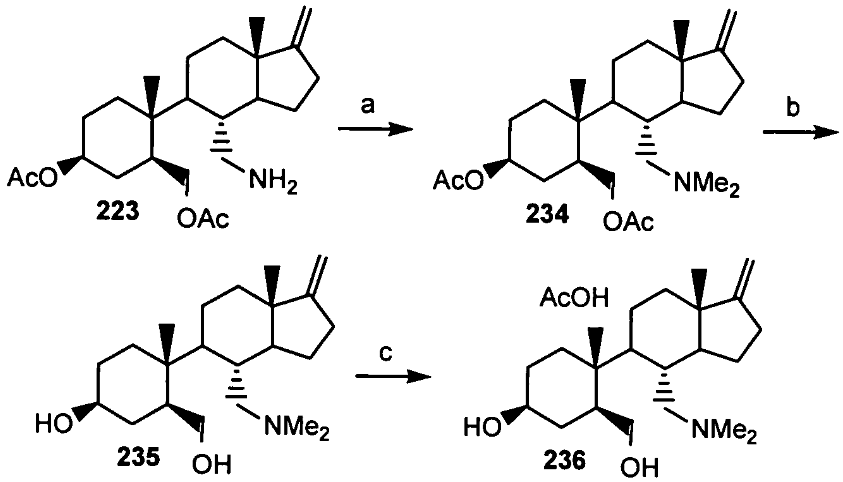
Synthesis of compound **229**

Using the procedures described for the synthesis of compound **232**, compound **229** (549 mg) was prepared as a glass-like solid in 36% yield starting from compound **226**. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 350.63; $C_{22}H_{40}NO_2$.

EXAMPLE 28

Compounds **235-236**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 28. Any number of compounds related to compounds **235-236** could be produced using similar methodology. Starting compound **223** may be prepared according to procedures described above in Example 25.

REACTION SCHEME 28



223 234 235 236

a) CH_2O, $NaBH_3CN$, MeCN; b) $LiAlH_4$, THF; c) 80% AcOH.

In general, reaction of an amino compound such as compound **223** with an aldehyde such as formaldehyde and a reducing agent such as $NaBH_3CN$ gives a tertiary amino compound such as compound **234**. A reducing agent such as lithium aluminum hydride is used to reduce the ester-protected hydroxyls to give compound **235**. Treatment with 80% acetic acid forms the ammonium acetate salt compound **236**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **234**</u>

$NaBH_3CN$ (2 x 25 mg, 0.8 mmol) was added over 25 minutes to a ambient temperature solution of compound **223** (99 mg, 0.24 mmol), 37% CH_2O in water (0.1 mL) and acetonitrile (2 mL). After 15 minutes the pH of the solution was adjusted to pH 7 by the dropwise addition of 80% acetic acid. After 1 hour the reaction mixture was diluted with EtOAc (150 mL) and was washed with saturated $NaHCO_3$ solution and brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/MeOH 95:5) to afford compound **234** (104 mg, 98%).

<u>Synthesis of compound **235**</u>

A solution of $LiAlH_4$ (5.5 mL of a 1.0 M solution in THF) was added to an

ice cooled solution of compound **234** (492 mg, 1.1 mmol) in THF (15 mL) under argon. After 25 minutes the cold bath was removed and the reaction was continued for 4 hours at ambient temperature. The reaction was cooled in ice and was quenched with $Na_2SO_4{\cdot}10H_2O$. After 10 minutes at ambient temperature, the solution was filtered, rinsing with EtOAc and the filtrate was washed with brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/MeOH/H_2O 16:3:1) to afford compound **235** (294 mg, 74%) as a crystalline solid.

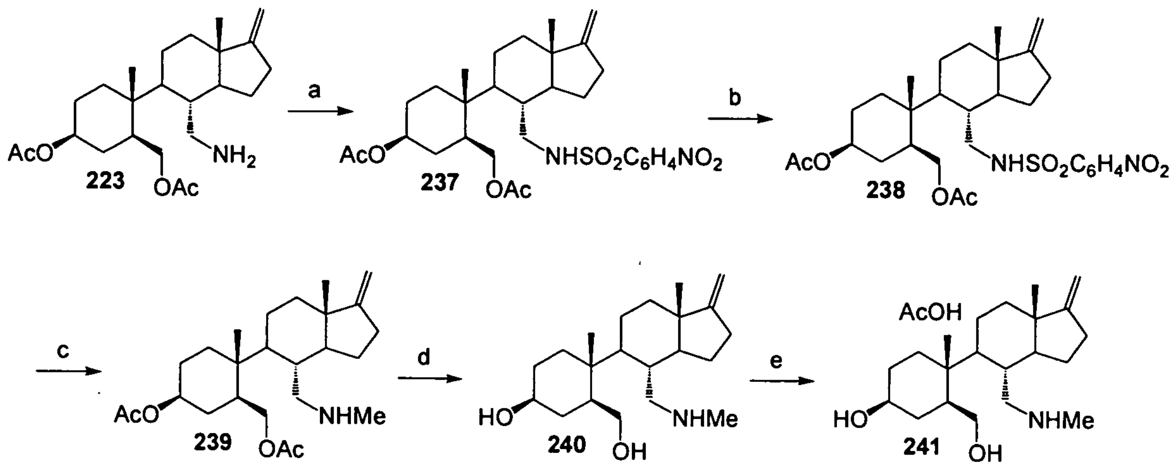
Synthesis of compound **236**

A solution of compound **235** (287 mg, 0.82 mmol) and 80% AcOH (10 mL) was stirred at 40°C for 10 minutes, then concentrated. Repeated concentration from a minimum of methanol in acetonitrile gave compound **236** (287 mg, 85%) as a white solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 350.69; $C_{22}H_{40}NO_2$.

EXAMPLE 29

Compounds **240-241**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 29. Any number of compounds related to compounds **240-241** could be produced using similar methodology. Starting compound **223** may be prepared according to procedures described above in Example 25.

REACTION SCHEME 29



a) 2-nitrobenzenesulfonyl chloride, Et_3N, CH_2Cl_2; b) MeI, K_2CO_3, DMF; c) PhSH, Cs_2CO_3, MeCN; d) KOH, H_2O, MeOH; e) 80% AcOH.

In general, an amino compound may be converted to a sulfonamide such as the reaction of compound **223** with a sulfonyl chloride such as 2-nitrobenzenesulfonyl chloride to give compound **237**. The sulfonamide nitrogen in a compound such as **237** may then be alkylated with an electrophile such as methyl iodide to give an amine compound such as **238**. The sulfonamide may be cleaved by reaction with a nucleophile such as the thiophenolate anion to give compound **239**. The acetates may be removed by base hydrolysis to give compound **240**. Treatment with 80% acetic acid forms the ammonium acetate salt compound **241**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **237**</u>

2-Nitrobenzenesulfonyl chloride (194 mg, 0.88 mmol) was added to an ice cooled solution of compound **223** (296 mg, 0.73 mmol), Et_3N (180 μL, 1.3 mmol) and CH_2Cl_2 (5 mL) under argon. After 30 minutes the cold bath was removed and the reaction was continued for 1 hour at ambient temperature. The reaction mixture was diluted with EtOAc and was washed with saturate $NaHCO_3$ solution and brine, then dried over $MgSO_4$, filtered and concentrated to afford compound **237** (433 mg, 100%) as a pale yellow solid.

Synthesis of compound **238**

MeI (60 µL and 2 x 30 µL, 1.9 mmol) was added over 7 hours to a solution of compound **237** (431 mg, 0.73 mmol), K_2CO_3 (232 mg, 1.7 mmol) and DMF (3 mL) under argon. After stirring overnight at ambient temperature, the reaction mixture was diluted with EtOAc and was washed with brine, then dried over $MgSO_4$, filtered and concentrated to give crude compound **238** that was used in the next step without further purification.

Synthesis of compound **239**

A solution of compound **238** (crude, 0.73 mmol), PhSH (225 µL, 2.19 mmol), $CsCO_3$ (714 mg, 2.19 mmol) and acetonitrile (6 mL) was heated at 55°C under argon for 1.5 hours. The ambient temperature reaction mixture was diluted with EtOAc and was washed with brine, then dried with $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexanes 1:1, then EtOAc/MeOH/Et_3N 90:10:2) to afford compound **239** (268 mg, 88%) as a pale yellow oil.

Synthesis of compound **240**

A solution of compound **239** (268 mg, 0.639 mmol), 10% KOH in water (1 mL) and MeOH (5 mL) was heated at 55°C for 4 hours. The ambient temperature reaction mixture was diluted with EtOAc (80 mL) and was washed with brine, then dried over $MgSO_4$, filtered and concentrated. The residue was purified by chromatography on silica gel (EtOAc/MeOH/H_2O/NH_4OH 80:15:5:1.5, then 70:20:10:2) to afford compound **240** (182 mg, 85%) as a white foam.

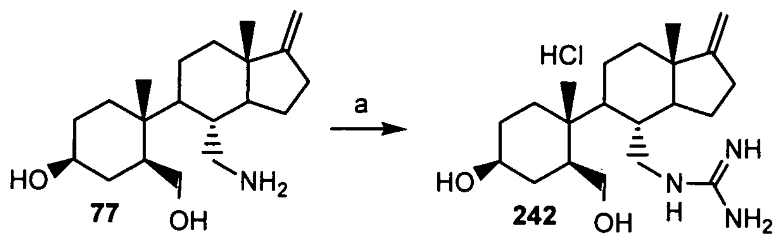
Synthesis of compound **241**

A solution of compound **240** (182 mg, 0.542 mmol) and 80% AcOH was heated at 40°C for 15 minutes, then concentrated. Residual solvent was removed by codistillation with methanol to afford compound **241** (210 mg, 98%) as a pale yellow foam. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 336.08; $C_{21}H_{38}NO_2$.

EXAMPLE 30

Compound **242**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 30. Any number of compounds related to compound **242** could be produced using similar methodology. Starting compound **77** may be prepared according to procedures described above in Example 8.

REACTION SCHEME 30



a) pyrazole-1-carboxamidine hydrochloride, DIEA, MeOH.

In general, reaction of an amino compound such as **77** with pyrazole-1-carboxamidine hydrochloride and diisopropylethylamine (DIEA) in methanol gives compound **242**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **242**</u>

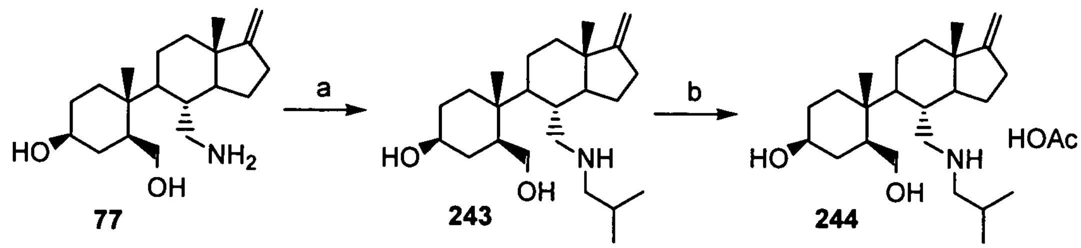
A solution of compound **77** (106 mg, 0.33 mmol), pyrazole-1-carboxamidine hydrochloride (51 mg, 0.35 mmol), DIEA (61 μl, 0.35 mmol) and MeOH (165 μl) was stirred at ambient temperature under argon for 3 days. The slurry was triturated in Et_2O, decanting off the solvent to give a white powder. The solid was then recrystallized from 3 ml of EtOAc/MeOH/Et_2O to afford compound **242** (64 mg, 48%) as a white solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 364.06; $C_{21}H_{38}N_3O_2$.

EXAMPLE 31

Compounds **243-250**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 31. Any number of compounds

related to compounds **243-250** could be produced using similar methodology. Starting compound **77** may be prepared according to procedures described above in Example 8.

REACTION SCHEME 31



a) Me_2CHCHO, $NaB(OAc)_3H$, 4A molecular sieves, 1,2-dichloroethane; b) 80% AcOH

In general, reductive amination of an amino compound such as compound **77** with a ketone or aldehyde such as isobutyraldehyde gives an amine such as compound **243**. Treatment with 80% acetic acid gives the salt compound 244.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **243**</u>

To a stirred mixture of compound **77** (100 mg, 0.31 mmol) in 1,2-dichloroethane (5 mL) and EtOH (1 mL) were added isobutyraldehyde (0.14 mL, 1.5 mmol), 4Å molecular sieves (100 mg), and $NaB(OAc)_3H$ (197 mg, 0.93 mmol). The mixture was stirred at ambient temperature for three days and then filtered through Celite and washed with EtOAc. The filtrate and washings were combined and concentrated. The residue was purified by column chromatography (EtOAc/MeOH, 9:1 then 8:2) to yield compound **243** (79 mg, 67%).

<u>Synthesis of compound **244**</u>

A solution of compound **243** (79 mg) in 80% HOAc (2 mL) was stirred at 40°C for a few minutes and then concentrated by rotary evaporation. The residue was codistilled with MeOH several times and dried under vacuum. The product was dissolved in a small amount of MeOH and treated with a small amount of acetonitrile. The solvents were removed and the product was dried under vacuum to give compound **244** (91 mg, 99%): LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7

water and MeCN) 378.21; $C_{24}H_{44}NO_2$.

Synthesis of compound **245**

Using the procedures described for the synthesis of compound **244**, with the exception of substitution by 1-methyl-4-piperidone, compound **245** (183 mg) was prepared in quantitative yield starting from compound **77**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 419.21; $C_{26}H_{47}N_2O_2$.

Synthesis of compound **246**

Using the procedures described for the synthesis of compound **244**, with the exception of substitution by 3-nitrobenzaldehyde, compound **246** (58 mg) was prepared in 35% yield starting from compound **77**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 457.22; $C_{27}H_{41}N_2O_4$.

Synthesis of compound **247**

Using the procedures described for the synthesis of compound **244**, with the exception of substitution by piperonal, compound **247** (161 mg) was prepared in 99% yield starting from compound **77**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 456.12; $C_{28}H_{42}NO_4$.

Synthesis of compound **248**

Using the procedures described for the synthesis of compound **244**, with the exception of substitution by pyrrole-2-carboxaldehyde, compound **248** (131 mg) was prepared in 91% yield starting from compound **77**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 401.15; $C_{25}H_{41}N_2O_2$.

Synthesis of compound **249**

Using the procedures described for the synthesis of compound **244**, with the exception of substitution by 2-furaldehyde, compound **249** (88 mg) was prepared in 61% yield starting from compound **77**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 402.23; $C_{25}H_{40}NO_3$.

Synthesis of compound **250**

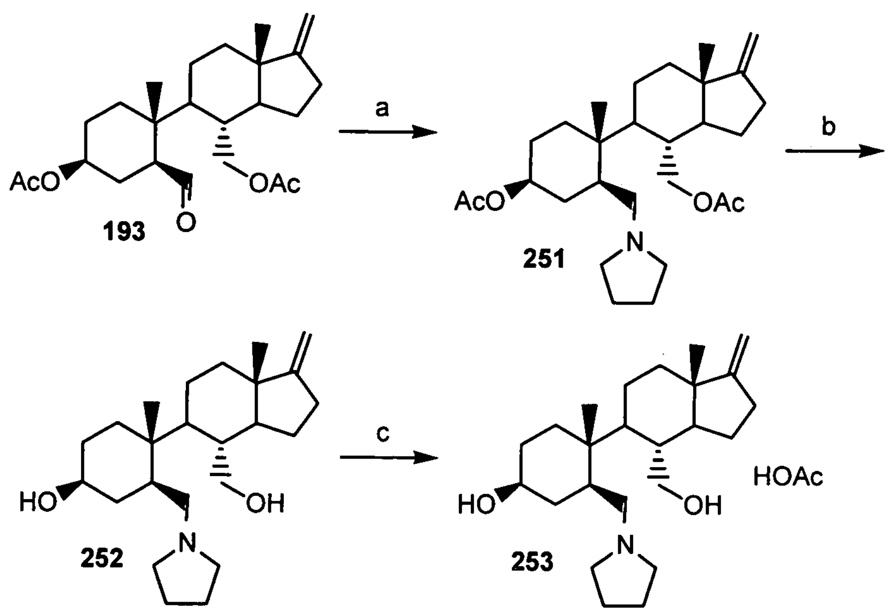
Using the procedures described for the synthesis of compound **244**, with

the exception of substitution by 3-pyridinecarboxaldehyde, compound **250** (59 mg) was prepared in 40% yield starting from compound **77**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 413.22; $C_{26}H_{41}N_2O_2$.

EXAMPLE 32

Compounds **252-261**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 32. Any number of compounds related to compounds **252-261** could be produced using similar methodology. Starting compound **193** may be prepared according to procedures described above in Example 9.

REACTION SCHEME 32



a) pyrrolidine, $NaB(OAc)_3H$, 4A molecular sieves, 1,2-dichloroethane; b) LAH, THF; c) 80% AcOH.

In general, reductive amination of a ketone or aldehyde compound such as compound **193** with an amine such as pyrrolidine gives an amine such as compound **251**. Lithium aluminum hydride reduction removes the acyl groups to give compound **252**. Treatment with 80% acetic acid gives the salt compound **253**.

Following are specific examples of the compounds prepared above.

Synthesis of compound **251**

To a stirred solution of compound **193** (150 mg, 0.37 mmol) in 1,2-dichloroethane (7.5 mL) were added pyrrolidine (0.18 mL, 2.2 mmol), 4Å molecular sieves (150 mg), and $NaB(OAc)_3H$ (314 mg, 1.5 mmol). The mixture was stirred at ambient temperature for three days and then filtered through Celite and washed with EtOAc. The filtrate and washings were combined and concentrated. The residue was purified by column chromatography (EtOAc/MeOH/Et_3N, 8:2:0.5) to yield compound **251** (155 mg, 91%).

Synthesis of compound **252**

To a stirred solution of compound **251** (155 mg, 0.34 mmol) in THF (15 mL) at 0°C was added 1M LAH in THF (1.7 mL, 1.7 mmol) dropwise. After 5 min at 0°C, the mixture was stirred at ambient temperature for 5 hours 40 min. The reaction was cooled to 0°C again and solid $Na_2SO_4.10H_2O$ (536 mg, 1.7 mmol) was added portionwise. After 5 min at 0°C, the mixture was stirred at ambient temperature for 1 hour and then filtered through Celite and washed with EtOAc. The filtrate and washings were combined and concentrated. The residue was purified by column chromatography (EtOAc/MeOH/water/Et_3N, 8:1:0.5:0.5) to yield compound **252** (121 mg, 92%).

Synthesis of compound **253**

A solution of compound **252** (121 mg) in 80% HOAc (2 mL) was stirred at 40°C for a few minutes and then concentrated by rotary evaporation. The residue was codistilled with MeOH several times and dried under vacuum. The product was dissolved in a small amount of MeOH and treated with a small amount of acetonitrile. The solvents were removed and the product was dried under vacuum to give compound **253** (147 mg, quant.): LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 376.24; $C_{24}H_{42}NO_2$.

Synthesis of compound **254**

Using the procedures described for the synthesis of compound **253**, with the exception of substitution by ethanolamine, compound **254** (84 mg) was prepared in 51% yield starting from compound **193**: LC/MS (direct infusion, electrospray +ve, 10

mM NH_4OAc in 3:7 water and MeCN) 366.13; $C_{22}H_{40}NO_3$.

Synthesis of compound **255**

Using the procedures described for the synthesis of compound **253**, with the exception of substitution by *N,N*-dimethylethylenediamine, compound **255** (38 mg) was prepared in 20% yield starting from compound **193**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 393.11; $C_{26}H_{49}N_2O_4$.

Synthesis of compound **256**

Using the procedures described for the synthesis of compound **253**, with the exception of substitution by cyclohexylamine, compound **256** (154 mg) was prepared in 87% yield starting from compound **193**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 404.28; $C_{26}H_{46}NO_2$.

Synthesis of compound **257**

Using the procedures described for the synthesis of compound **253**, with the exception of substitution by 3-(aminomethyl)pyridine, compound **257** (122 mg) was prepared in 65% yield starting from compound **193**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 413.15; $C_{26}H_{41}N_2O_2$.

Synthesis of compound **258**

Using the procedures described for the synthesis of compound **253**, with the exception of substitution by furfurylamine, compound **258** (83 mg) was prepared in 47% yield starting from compound **193**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 402.20; $C_{25}H_{40}NO_3$.

Synthesis of compound **259**

Using the procedures described for the synthesis of compound **253**, with the exception of substitution by 3-fluoroaniline and no salt formation step, compound **259** (86 mg) was prepared in 57% yield starting from compound **193**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 416.08; $C_{26}H_{39}FNO_2$.

Synthesis of compound **260**

Using the procedures described for the synthesis of compound **259**, with the exception of substitution by 3-aminopyridine, compound **260** (42 mg) was prepared in 28% yield starting from compound **193**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 399.20; $C_{25}H_{39}N_2O_2$.

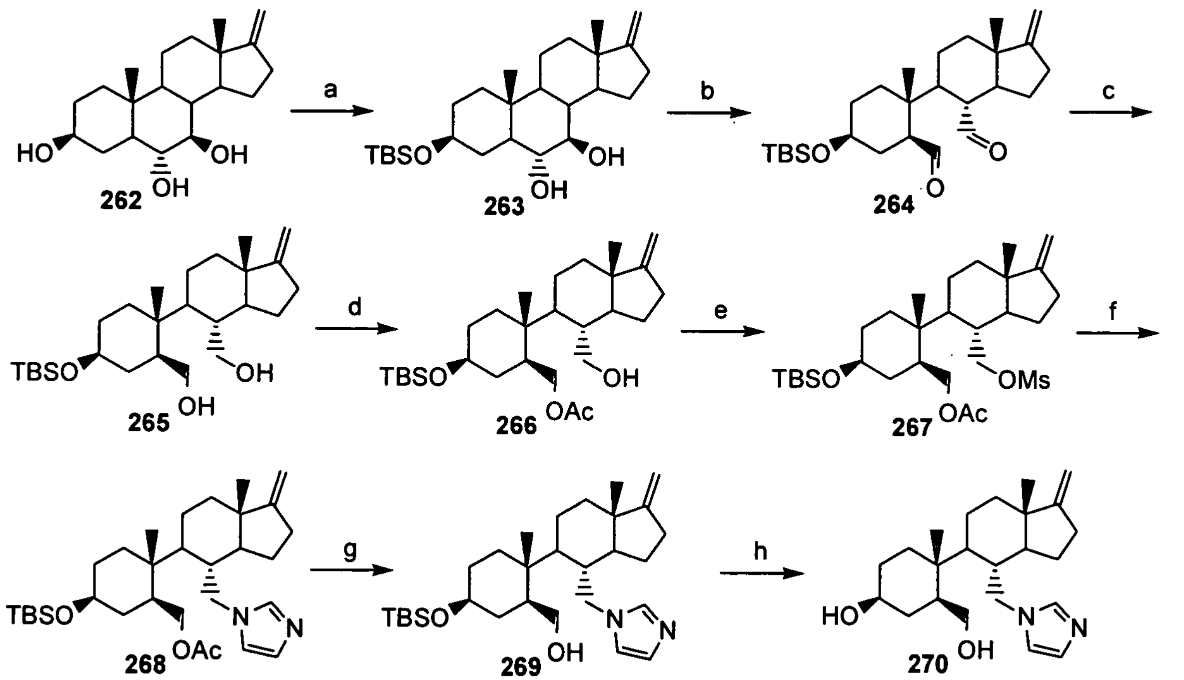
Synthesis of compound **261**

Using the procedures described for the synthesis of compound **259**, with the exception of substitution by *m*-toluidine, compound **261** (91 mg) was prepared in 60% yield starting from compound **193**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 412.20; $C_{27}H_{42}NO_2$.

EXAMPLE 33

Compound **270**, a representative compound of the invention, may be prepared according to the following Reaction Scheme 33. Any number of compounds related to compound **270** could be produced using similar methodology. Starting compound **262** may be prepared according to procedures described in U.S. Patent 6,046,185.

REACTION SCHEME 33



a) TBSCl, imidazole, DMAP, DMF, THF; b) $NaIO_4$, H_2O, THF; c) $NaBH_4$, MeOH, THF; d) Ac_2O, DMAP, pyridine; e) MsCl, pyridine; f) NaH, imidazole, DMF; g) LAH, THF; h) HOAc.

In general, treatment with TBSCl and imidazole in DMF selectively protects one hydroxyl to give compound **263**. $NaIO_4$ oxidation gives the dialdehyde compound **264**. Sodium borohydride reduction gives compound **265**. Reaction with acetic anhydride and DMAP in pyridine selectively protects one hydroxyl to give compound **266**. The free hydroxyl is reacted to give the mesylate compound **267** using MsCl and pyridine. Displacement of the mesylate by the anion of imidazole in DMF gives compound **268**. Lithium aluminum hydride removes the acyl group to give compound **269**. Treatment with 80% acetic acid removes the TBS group to give compound **270**.

Following are specific examples of the compounds prepared above.

Synthesis of compound 263

To a solution of crude compound **262** (86.3 mmol) in DMF (90 mL) and THF (150 mL) that was cooled in a cold water bath were added DMAP (0.50 g, 4.1 mmol), imidazole (11.8 g, 173 mmol) and TBSCl (15.6 g, 104 mmol). The mixture was

stirred at ambient temperature for 2.5 hours, then cooled in a cold water bath. Water (100 mL) and EtOAc (100 mL) were added. The layers were separated and the aqueous portion was back-extracted with EtOAc (50 mL). The combined organics were washed with brine (2 x 250 mL), dried over anhydrous $MgSO_4$ and concentrated to dryness to give compound **263** (38.0 g, quantitative) as a white foam.

Synthesis of compound **264**

To a solution of compound **263** (38.0 g, 86.3 mmol) in THF (250 mL) that was cooled in a cold water bath was added a slurry of $NaIO_4$ (36.9 g, 173 mmol) in water (120 mL). The reaction mixture was stirred at ambient temperature for 1.5 hours, then water (150 mL) and EtOAc (150 mL) were added. The layers were separated and the aqueous portion was back-extracted with EtOAc (100 mL). The combined organics were washed with brine (200 mL), dried over anhydrous $MgSO_4$ and concentrated to dryness to give crude compound **264** that was used in the next step without further purification.

Synthesis of compound **265**

To a solution of crude compound **264** (86.3 mmol) in THF (125 mL) and MeOH (125 mL) at 0°C was added $NaBH_4$ (6.53 g, 173 mmol) in portions. The mixture was stirred at 0°C for 15 minutes, then at ambient temperature for 1 hour. The mixture was cooled in a cold water bath and quenched with 80% acetic acid until pH = 7.0. Water (100 mL) and EtOAc (150 mL) were added. The layers were separated and the aqueous portion was back-extracted with EtOAc (100 mL). The combined organics were washed with brine (200 mL), dried over anhydrous $MgSO_4$ and concentrated to dryness. The residue was stirred with hexanes (150 mL) for 2 hours, then the precipitate was filtered out, rinsing with hexanes (2 x 25 mL). The solid was dried to afford compound **265** (19.8 g, 52% from compound **263**) as a white solid.

Synthesis of compound **266**

To a solution of compound **265** (17.0 g, 38.9 mmol) in CH_2Cl_2 (25 mL) and pyridine (50 mL) that was cooled in a cold water bath were added DMAP (0.50 g, 4.1 mmol), then acetic anhydride (4.0 mL, 43 mmol) dropwise. The mixture was stirred at

ambient temperature for 1.5 hours. Brine (120 mL) and EtOAc (250 mL) were added. The layers were separated and the aqueous portion was back-extracted with EtOAc (100 mL). The combined organics were washed with brine (2 x 150 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 49:1, 19:1, 9:1, 4:1) to give compound **266** (11.0 g, 59%) as a white solid.

Synthesis of compound **267**

To a stirred solution of compound **266** (2.4 g, 5.0 mmol) in pyridine (20 mL) was added MsCl (0.39 mL, 5.0 mmol) dropwise. The resulting mixture was stirred at ambient temperature for 5 hours. The mixture was diluted with EtOAc (300 mL), washed with brine, and the aqueous washings were combined and extracted with EtOAc. The organic extracts were combined and washed with brine, dried and concentrated to yield compound **267** (2.8 g, 100%) as a pale solid.

Synthesis of compound **268**

To a stirred solution of imidazole (66 mg, 0.97 mmol) in DMF (6 mL) at ambient temperature was added NaH (39 mg, 60% in mineral oil, 0.97 mmol). After stirring for 1 hour at ambient temperature, the mixture became clear and compound **267** (200 mg, 0.36 mmol) was added as solid. The mixture was stirred at 60°C for 3 hours 45 min and then left at ambient temperature overnight. The mixture was diluted with toluene (200 mL), washed with brine, dried and concentrated. The crude compound **268** was used in next step without purification.

Synthesis of compound **269**

To a stirred solution of compound **268** (0.36 mmol) in THF (15 mL) at 0°C was added 1M LAH in THF (0.57 mL, 0.57 mmol) dropwise. After 5 minutes at 0°C, the mixture was stirred at ambient temperature for 5 hours. The reaction was cooled to 0°C again and solid $Na_2SO_4.10H_2O$ (184 mg, 0.57 mmol) was added portionwise. After 5 min at 0°C, the mixture was stirred at ambient temperature for 1 hour and then filtered through Celite and washed with EtOAc. The filtrate and washings were combined and concentrated. The crude compound **269** was used in next step without purification

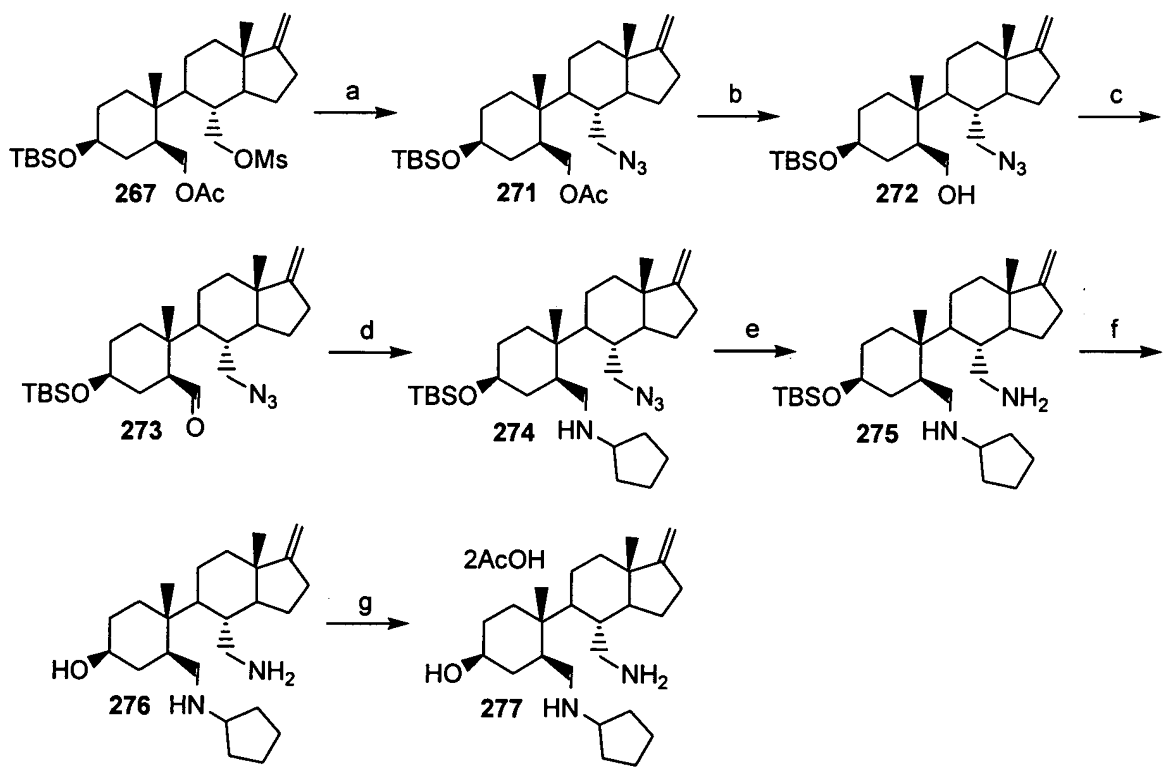
<u>Synthesis of compound **270**</u>

A solution of crude compound **269** (0.36 mmol) in 80% HOAc (4 mL) was stirred at 40°C for 6.5 hours. The solvents were removed and the residue was purified with column chromatography (EtOAc/MeOH/Et_3N, 8:1.5:0.5) to afford compound **270** (110 mg, 82% from compound **267**). LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 372.87; $C_{23}H_{37}N_2O_2$.

EXAMPLE 34

Compounds **276-277**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 34. Any number of compounds related to compounds **276-277** could be produced using similar methodology. Starting compound **267** may be prepared according to procedures described above in Example 33.

REACTION SCHEME 34



a) NaN_3, DMF; b) K_2CO_3, MeOH, H_2O; c) NMO, TPAP, CH_2Cl_2; d) cyclopentylamine, $NaB(OAc)_3H$, 4A molecular sieves, 1,2-dichloroethane; e) LAH, THF; f) 80% AcOH; g) 80% AcOH

In general, azide displacement of the mesylate by NaN_3 in DMF gives compound **271**. Base hydrolysis of the acetate gives compound **272**. TPAP catalyzed oxidation of the hydroxyl group gives compound **273**. Reductive amination with cyclopentylamine gives compound **274**. Lithium aluminum hydride reduces the azide to give compound **275**. Treatment with 80% acetic acid removes the TBS group to give compound **276**. After column purification, further treatment with 80% acetic acid gives the salt compound **277**.

Following are specific examples of the compounds prepared above.

Synthesis of compound **271**

A mixture of compound **267** (1.8 g, 3.2 mmol) and NaN_3 (420 mg, 6.5 mmol) in DMF (26 mL) was stirred at 60°C overnight. The mixture was cooled to ambient temperature and diluted with toluene (300 mL), washed with brine, dried and concentrated to give compound **271** (1.56 g, 95%).

Synthesis of compound **272**

A mixture of compound **271** (1.35 g, 2.68 mmol), K_2CO_3 (2.9 g, 21 mmol) in MeOH/THF/water (50 mL/50 mL/39 mL) was stirred at ambient temperature overnight. Most of the solvents were removed by rotary evaporation and the residue was diluted with water (250 mL) and extracted with EtOAc. The EtOAc extracts were combined and washed with brine, dried and concentrated. The crude product was purified by column chromatography (hexanes/EtOAc, 85:15) to give compound **272** (856 mg) in 69% yield.

Synthesis of compound **273**

To a stirred solution of compound **272** (892 mg, 1.93 mmol) in CH_2Cl_2 (35 mL) was added NMO (333 mg, 2.84 mmol) and TPAP (57 mg, 0.16 mmol). The mixture was stirred at ambient temperature for 2 hours 15 min and then the solvent was removed by rotary evaporation. The residue was purified by column chromatography (hexanes/EtOAc, 9:1) to give compound **273** (769 mg) in 87% yield.

Synthesis of compound **274**

To a stirred solution of compound **273** (170 mg, 0.37 mmol) in 1,2-

dichloroethane (8 mL) were added cyclopentylamine (0.18 mL, 1.8 mmol), 4Å molecular sieves (170 mg), and $NaB(OAc)_3H$ (331 mg, 1.56 mmol). The mixture was stirred at ambient temperature for 28 hours and then filtered through Celite and washed with EtOAc. The filtrate and washings were combined and concentrated. The residue was filtered through silica column with EtOAc/MeOH (9:1), and the crude compound **274** was used in next step without further purification.

<u>Synthesis of compound **275**</u>

To a stirred solution of compound **274** (0.37 mmol) in THF (15 mL) at 0°C was added 1M LAH in THF (1.9 mL, 1.9 mmol) dropwise. After 5 min at 0°C, the mixture was stirred at ambient temperature for 5.5 hours. The reaction was cooled to 0°C again and solid $Na_2SO_4.10H_2O$ (596 mg, 1.9 mmol) was added portionwise. After 5 min at 0°C, the mixture was stirred at ambient temperature for 1 hour and then filtered through Celite and washed with EtOAc. The filtrate and washings were combined and concentrated. The crude compound **275** was used in next step without purification.

<u>Synthesis of compound **276**</u>

A solution of crude compound **275** (0.37 mmol) in 80% HOAc (5 mL) was stirred at 40°C for 7.5 hours. The solvents were removed and the residue was purified by column chromatography (EtOAc/MeOH/water/Et_3N, 6.5:2.5:0.5:0.5) to afford compound **276** (74 mg, 52% from compound **273**).

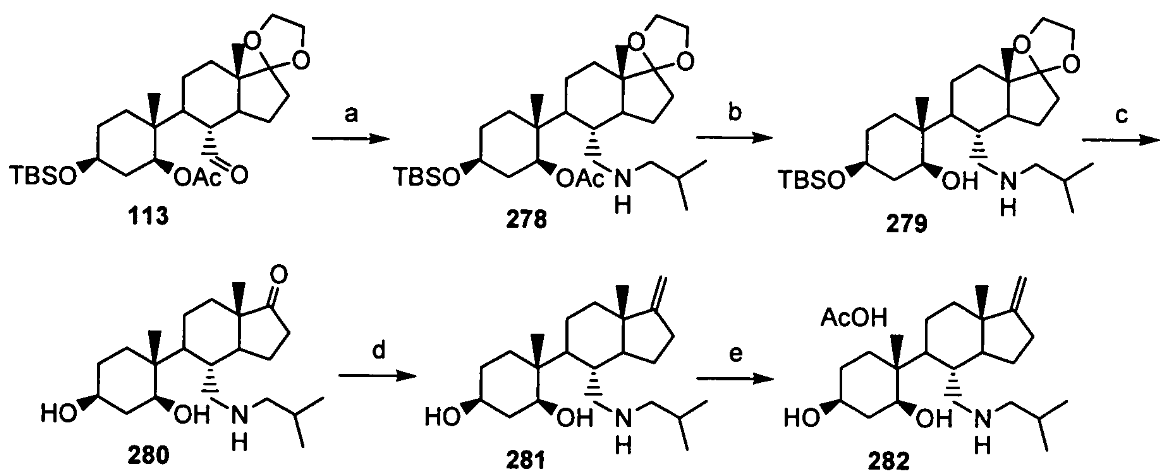
<u>Synthesis of compound **277**</u>

A solution of compound **276** (74 mg) in 80% HOAc (0.5 mL) was stirred at ambient temperature for a few minutes and then the solvents were removed by rotary evaporation. The residue was co-evaporated with MeOH several times and dried under vacuum. The product was dissolved in a small amount of MeOH and treated with a small amount of acetonitrile. The solvents were removed and the product was dried under vacuum to afford compound **277** (90 mg, 93%) as off-white powder: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 388.98; $C_{25}H_{45}N_2O$.

EXAMPLE 35

Compounds **282-306**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 35. Any number of compounds related to compounds **282-306** could be produced using similar methodology. Starting compound **113** may be prepared according to procedures described above in Example 12.

REACTION SCHEME 35



a) isobutylamine, $NaB(OAc)_3H$, 4 Å MS, DCE; b) $LiAlH_4$, THF; c) 80% AcOH, 40°C; d) $MePPh_3Br$, KO^tBu, THF; e) 80% AcOH.

In general, reductive amination of a ketone or aldehyde compound such as compound **113** with an amine such as isobutylamine gives an amine such as compound **278**. Lithium aluminum hydride reduction removes the acyl group to give compound **279**. Treatment with 80% acetic acid removes both the TBS group and the cyclic ketal to give compound **280**. Olefination using $MePPh_3Br$ and KO^tBu in THF gives compound **281**. Treatment with 80% acetic acid gives the salt compound **282**.

Following are specific examples of the compounds prepared above.

<u>Synthesis of compound **278**</u>

A mixture of compound **113** (0.18 g, 0.35 mmol), isobutylamine (0.18 mL, 1.8 mmol) and 4 Å molecular sieves (0.15 g) in DCE (5 mL) was stirred at ambient temperature for 1 hour. $NaB(OAc)_3H$ (0.395 g, 1.77 mmol) was added and the mixture

was stirred at ambient temperature for 5 days. The reaction mixture was diluted with MeOH and filtered through a celite bed, rinsing with EtOAc. The filtrate was washed with saturated $NaHCO_3$ solution then brine twice, dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel to give a mixture of compound **278** and the imine of compound **278** (0.240 g) as a light yellow oil that was used in the next reaction without further purification.

<u>Synthesis of compound **279**</u>

To a solution of the mixture of compound **278** and its imine (0.33 mmol) in THF (10 mL) was added $LiAlH_4$ (0.99 mL of a 1 M solution in THF, 0.99 mmol). The mixture was stirred at ambient temperature overnight then quenched with $Na_2SO_4 \cdot 10H_2O$ and stirred for 30 minutes. The mixture was filtered, rinsing with EtOAc, and concentrated to dryness to give crude compound **279** (0.137 g) as a colourless glass that was used in the next reaction without further purification.

<u>Synthesis of compound **280**</u>

Crude compound **279** (0.33 mmol) was dissolved in 80% acetic acid (7 mL) and stirred at 40°C overnight then concentrated. The residue was partially purified by chromatography on silica gel to give compound **280** (0.083 g) as a colourless glass.

<u>Synthesis of compound **281**</u>

A mixture of KO^tBu (0.184 g, 1.56 mmol) and $MePPh_3Br$ (0.557 g, 1.56 mmol) in THF (6 mL) was stirred at ambient temperature for 1.5 hours, then a solution of compound **281** (0.083 g, 0.20 mmol) in THF (4 mL) was added. The reaction mixture was stirred at ambient temperature overnight then quenched with saturated NH_4Cl solution and concentrated. The residue was partially purified by chromatography on silica gel to afford compound **281** that was used for the next reaction.

<u>Synthesis of compound **282**</u>

A mixture of compound **281** (0.2 mmol), 80% AcOH and MeOH was concentrated by rotary evaporation. The residue was dissolved in water and washed with CH_2Cl_2 (5 x 5 mL) then concentrated. Precipitation from hexanes afforded compound **282** (0.042 g, 28% from compound **113**) as a white solid: LC/MS (direct

infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 364.22; $C_{23}H_{42}NO_2$.

Synthesis of compound **283**

Using the procedure described for the synthesis of compound **278**, with the exceptions that 0.329 g (1.47 mmol) $NaB(OAc)_3H$ were used and the reaction time was 4 days, compound **113** (0.25 g, 0.49 mmol) was reacted with 3-(aminomethyl)pyridine (0.25 mL, 2.5 mmol) to give imine intermediate (0.225 g, 77%, white foam). Using the procedure described for the synthesis of compound **279**, with the exception that reaction time was 5 hours, the imine intermediate (0.376 mmol) was reacted with $LiAlH_4$ (1.50 mL of a 1 M solution in Et_2O, 1.50 mmol) to give crude alcohol intermediate with TBS cleaved (0.162 g, yellow foam). Using the procedure described for the synthesis of compound **280**, with the exceptions that 20 mL 80% AcOH were used and the reaction was performed at ambient temperature, the crude alcohol intermediate mixture (0.376 mmol) was converted to ketone intermediate (0.095 g, colourless glass). Using the procedure described for the synthesis of compound **281**, with the exceptions that 0.163 g (1.38 mmol) KO^tBu and 0.492 g (1.38 mmol) $MePPh_3Br$ were used and after quenching the reaction mixture was filtered through celite, the ketone intermediate (0.23 mmol) was converted to the alkene. Precipitation from Et_2O afforded compound **283** (0.014 g, 7% from compound **113**) as a white solid. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 397.75; $C_{25}H_{38}N_2O_2$.

Synthesis of compound **284**

Using the procedure described for the synthesis of compound **278**, compound **113** (0.18 g, 0.35 mmol) was reacted with ethanolamine (0.11 mL, 1.8 mmol) to give amine intermediate (0.053 g, 27%, yellow oil). Using the procedure described for the synthesis of compound **279**, the amine intermediate (0.096 mmol) was reacted with $LiAlH_4$ (0.19 mL of a 1 M solution in THF, 0.19 mmol) to give the alcohol intermediate with some TBS cleavage (0.040 g, colourless glass). Using the procedure described for the synthesis of compound **280**, with the exceptions that 6 mL 80% acetic acid were used and the residue was not purified, the crude alcohol intermediate mixture

was converted to ketone intermediate as the acetic acid salt (0.041 g, colourless glass). Using the procedure described for the synthesis of compound **281**, the ketone intermediate (0.096 mmol) was converted to the crude alkene. Using the procedure described for the synthesis of compound **282**, with the exception that the residue was not washed with CH_2Cl_2, the crude alkene was converted to the acetic acid salt. Precipitation from hexanes/CH_2Cl_2 afforded compound **284** (0.015 g, 10% from compound **113**) as a yellow solid. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 352.12; $C_{21}H_{38}NO_3$.

Synthesis of compound **285**

Using the procedure described for the synthesis of compound **278**, with the exceptions that 0.20 g 4 Å molecular sieves were used, the reaction began with 0.395 g (1.77 mmol) $NaB(OAc)_3H$, then 0.263 g (1.18 mmol) more $NaB(OAc)_3H$ was added after 2 days and the total reaction time was 6 days, compound **113** (0.30 g, 0.59 mmol) was reacted with furfurylamine (0.27 mL, 3.0 mmol) to give a mixture of amine and imine intermediates (0.283 g, white foam). Using the procedure described for the synthesis of compound **279**, with the exception that reaction time was 5 hours, the amine/imine intermediate mixture (0.48 mmol) was reacted with $LiAlH_4$ (1.44 mL of a 1 M solution in Et_2O, 1.44 mmol) to give crude alcohol intermediate with most TBS cleaved (0.248 g, yellow oil). Using the procedure described for the synthesis of compound **280**, with the exceptions that 20 mL 80% AcOH were used, the reaction was performed at ambient temperature and the residue after purification was dissolved in THF (6 mL) and treated with 2 N HCl (2 mL) at ambient temperature overnight then concentrated, the crude alcohol intermediate mixture (0.481 mmol) was converted to ketone intermediate as the HCl salt (0.146 g, yellow oil). Using the procedure described for the synthesis of compound **281**, with the exceptions that 0.236 g (2.00 mmol) KO^tBu and 0.715 g (2.00 mmol) $MePPh_3Br$ were used, DMF (0.5 mL) was added and after quenching the reaction mixture was filtered through celite, the ketone intermediate (0.33 mmol) was converted to the crude alkene. Using the procedure described for the synthesis of compound **282**, the crude alkene was converted to the acetic acid salt.

Precipitation from Et_2O afforded compound **285** (0.013 g, 14% from compound **113**) as a light brown solid. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 388.16; $C_{24}H_{38}NO_3$.

<u>Synthesis of compound **286**</u>

Using the procedure described for the synthesis of compound **278**, with the exception that the residue was not purified, compound **113** (0.18 g, 0.35 mmol) was reacted with *N,N*-dimethylethylenediamine (0.20 mL, 1.8 mmol) to give a mixture of amine and imine intermediates (0.192 g, colourless oil). Using the procedure described for the synthesis of compound **279**, the amine/imine intermediate mixture (0.33 mmol) was reacted with $LiAlH_4$ (0.99 mL of a 1 M solution in THF, 0.99 mmol) to give crude alcohol intermediate (0.137 g, colourless glass). Using the procedure described for the synthesis of compound **280**, with the exception that the residue was not purified, the crude alcohol intermediate was converted to ketone intermediate as the acetic acid salt (0.147 g, colourless glass). Using the procedure described for the synthesis of compound **281**, the ketone intermediate (0.33 mmol) was converted to the crude alkene. Using the procedure described for the synthesis of compound **282**, with the exception that the residue was not washed with CH_2Cl_2, the crude alkene was converted to the acetic acid salt. Concentration from CH_2Cl_2 afforded compound **286** (0.072 g, 47% from compound **113**) as a light yellow solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 379.03; $C_{23}H_{43}N_2O_2$.

<u>Synthesis of compound **287**</u>

Using the procedure described for the synthesis of compound **278**, compound **113** (0.18 g, 0.35 mmol) was reacted with 2-(1-cyclohexenyl)ethylamine (0.25 mL, 1.8 mmol) to give amine intermediate (0.165 g, 77%, yellow oil). Using the procedure described for the synthesis of compound **279**, the amine intermediate (0.27 mmol) was reacted with $LiAlH_4$ (0.53 mL of a 1 M solution in THF, 0.53 mmol) to give crude alcohol intermediate (0.132 g, colourless glass). Using the procedure described for the synthesis of compound **280**, with the exception that 8 mL 80% acetic acid were used, the crude alcohol intermediate was converted to ketone intermediate as the acetic

acid salt (0.108 g, colourless glass). Using the procedure described for the synthesis of compound **281**, the ketone intermediate (0.23 mmol) was converted to the crude alkene. Using the procedure described for the synthesis of compound **282**, with the exception that the residue was washed with Et_2O (4 x 5 mL) instead of CH_2Cl_2, the crude alkene was converted to the acetic acid salt. Precipitation from hexanes/CH_2Cl_2 afforded compound **287** (0.051 g, 31% from compound **113**) as a white solid: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 416.26; $C_{27}H_{46}NO_2$.

Synthesis of compound **288**

Using the procedure described for the synthesis of compound **278**, with the exception that the residue was not purified, compound **113** (0.18 g, 0.35 mmol) was reacted with 4-(2-aminoethyl)morpholine (0.23 mL, 1.8 mmol) to give the amine intermediate (0.205 g, 94%, colourless oil). Using the procedure described for the synthesis of compound **279**, the amine intermediate (0.33 mmol) was reacted with $LiAlH_4$ (0.66 mL of a 1 M solution in THF, 0.66 mmol) to give crude alcohol intermediate (0.150 g, colourless glass). Using the procedure described for the synthesis of compound **280**, with the exceptions that 8 mL 80% acetic acid were used and the residue was not purified, the crude alcohol intermediate was converted to ketone intermediate as the acetic acid salt (0.203 g, brown oil). Using the procedure described for the synthesis of compound **281**, the ketone intermediate (0.33 mmol) was converted to the crude alkene. Using the procedure described for the synthesis of compound **282**, with the exception that the residue was purified by chromatography on silica gel after washing, the crude alkene was converted to the acetic acid salt. Precipitation from Et_2O afforded compound **288** (0.108 g, 64% from compound **113**) as an off-white solid. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 421.16; $C_{25}H_{45}N_2O_3$.

Synthesis of compound **289**

Using the procedure described for the synthesis of compound **278**, with the exceptions that 0.125 g 4 Å molecular sieves were used, the reaction began with

0.329 g (1.47 mmol) $NaB(OAc)_3H$, then 0.219 g (0.982 mmol) more $NaB(OAc)_3H$ was added after 2 days and the total reaction time was 6 days, compound **113** (0.25 g, 0.49 mmol) was reacted with *m*-toluidine (0.27 mL, 2.5 mmol) to give amine intermediate (0.240 g, yellow oil). Using the procedure described for the synthesis of compound **279**, with the exception that reaction time was 5 hours, the amine intermediate (0.400 mmol) was reacted with $LiAlH_4$ (0.80 mL of a 1 M solution in Et_2O, 0.80 mmol) to give crude alcohol intermediate with most TBS cleaved (0.224 g, yellow oil). Using the procedure described for the synthesis of compound **280**, with the exceptions that 20 mL 80% AcOH were used and the reaction was performed at ambient temperature, the crude alcohol intermediate mixture (0.400 mmol) was converted to ketone intermediate (0.135 g, light brown solid). Using the procedure described for the synthesis of compound **281**, with the exceptions that 0.238 g (2.01 mmol) KO^tBu and 0.719 g (2.01 mmol) $MePPh_3Br$ were used and after quenching the reaction mixture was filtered through celite, the ketone intermediate (0.34 mmol) was converted to the alkene. Concentration from CH_2Cl_2 gave compound **289** (0.095 g, 49% from compound **113**) as a yellow foam.

Synthesis of compound **290**

Using the procedure described for the synthesis of compound **278**, with the exceptions that 0.10 g 4 Å molecular sieves and 6 mL DCE were used, the reaction began with 0.165 g (0.740 mmol) $NaB(OAc)_3H$, then 0.083 g (0.37 mmol) more $NaB(OAc)_3H$ was added after 8 hours and the total reaction time was 2 days, compound **113** (0.197 g, 0.387 mmol) was reacted with benzylamine (0.21 mL, 1.9 mmol) to give amine intermediate (0.171 g, 73%, colourless gum). Using the procedure described for the synthesis of compound **279**, with the exceptions that 6 mL THF were used and reaction time was 5 hours, the amine intermediate (0.28 mmol) was reacted with $LiAlH_4$ (0.56 mL of a 1 M solution in THF, 0.56 mmol) to give crude alcohol intermediate with TBS cleaved (0.132 g, colourless gum). Using the procedure described for the synthesis of compound **280**, with the exceptions that the alcohol was treated with 2 N HCl (2 mL) in THF (6 mL) instead of 80% acetic acid and the reaction was performed at ambient temperature, the crude alcohol intermediate mixture (0.28 mmol) was

converted to ketone intermediate (0.095 g, colourless glass). Using the procedure described for the synthesis of compound **281**, with the exceptions that 0.162 g (1.44 mmol) KO^tBu, 0.514 g (1.44 mmol) $MePPh_3Br$ and 13 mL THF were used and after quenching the reaction mixture was diluted with EtOAc (20 mL) and MeOH (10 mL) then filtered through celite, the ketone intermediate (0.24 mmol) was converted to the alkene. Precipitation from ACN gave compound **290** (0.063 g, 41% from compound **113**) as a white solid. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 382.06; $C_{25}H_{36}NO_2$.

Synthesis of compound **291**

Using the procedures described for the synthesis of compound **282**, with the exception of substitution by 3-fluorobenzylamine, compound **291** (0.039 g) was prepared as a yellow solid in 23% yield starting from compound **95**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 416.21; $C_{26}H_{39}FNO_2$.

Synthesis of compound **292**

Using the procedures described for the synthesis of compound **282**, with the exception of substitution by morpholine, compound **292** (0.089 g) was prepared as a light pink solid in 58% yield starting from compound **95**. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 378.12; $C_{23}H_{40}NO_3$.

Synthesis of compound **293**

Using the procedures described for the synthesis of compound **282**, with the exception of substitution by 3,4-(methylenedioxy)aniline, compound **293** (0.068 g) was prepared as a white solid in 45% yield starting from compound **95**. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 428.37; $C_{26}H_{38}NO_4$.

Synthesis of compound **294**

Using the procedures described for the synthesis of compound **282**, with the exception of substitution by isobutylamine, compound **294** (0.111 g) was prepared as a orange solid in 75% yield starting from compound **95**. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 364.12; $C_{23}H_{42}NO_2$.

Synthesis of compound **295**

Using the procedures described for the synthesis of compound **282**, with the exception of substitution by cyclohexylamine, compound **295** (0.029 g) was prepared as a orange solid in 18% yield starting from compound **95**. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 390.12; $C_{25}H_{42}NO_2$.

Synthesis of compound **296**

Using the procedures described for the synthesis of compound **282**, with the exception of substitution by *N*-methylaniline, compound **296** (0.040 g) was prepared as a orange solid in 28% yield starting from compound **95**. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 397.86; $C_{26}H_{40}NO_2$.

Synthesis of compound **297**

Using the procedure described for the synthesis of compound **278**, with the exceptions that 0.20 g of 4 Å molecular sieves and 7 mL DCE were used, the mixture was stirred for 1 hour before $NaB(OAc)_3H$ was added, reaction time was 3 days and the residue was purified by chromatography on silica gel (hexanes/EtOAc, 1:1; EtOAc/MeOH, 9:1), compound **95** (0.25 g, 0.49 mmol) was reacted with 3-(aminomethyl)pyridine (0.25 mL, 2.5 mmol) to give amine intermediate (0.266 g, 90%, colourless glass). Using the procedure described for the synthesis of compound **279**, with the exception that reaction time was overnight, the amine intermediate (0.44 mmol) was reacted with $LiAlH_4$ (0.98 mL of a 1 M solution in Et_2O, 0.98 mmol) to give alcohol intermediate (0.255 g, yellow foam). Using the procedure described for the synthesis of compound **280**, with the exceptions that 20 mL 80% AcOH were used, the reaction was run at ambient temperature for 4 days and the product was residue was purified by chromatography on silica gel ($EtOAc/MeOH/H_2O/Et_3N$, 9:1:0.25:0.25), the alcohol intermediate (0.46 mmol) was converted to ketone intermediate as the free amine (0.039 g, light brown solid). Using the procedure described for the synthesis of compound **281**, with the exceptions that 0.069 g (0.58 mmol) KO^tBu, 0.209 g, (0.585 mmol) $MePPH_3Br$ and 7 mL THF were used, the reaction was stirred for 1 hour before the ketone intermediate solution was added and reaction time was 2 days, the ketone

intermediate (0.097 mmol) was converted to the crude alkene. Using the procedure described for the synthesis of compound **282**, with the exception that the residue was not purified by chromatography, the crude alkene was converted to compound **297** (0.011 g, 5% from INT1703) as a yellow glass. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 399.16; $C_{25}H_{39}N_2O_2$.

<u>Synthesis of compound **298**</u>

Using the procedure described for the synthesis of compound **278**, with the exceptions that 0.20 g of 4 Å molecular sieves and 7 mL DCE were used, the mixture was stirred for 1 hour before $NaB(OAc)_3H$ was added, reaction time was 3 days and the residue was purified by chromatography on silica gel (hexanes/EtOAc, 3:2, 1:1), compound **95** (0.25 g, 0.49 mmol) was reacted with furfurylamine (0.23 mL, 2.5 mmol) to give amine intermediate (0.269 g, 93%, yellow foam). Using the procedure described for the synthesis of compound **279**, the amine intermediate (0.46 mmol) was reacted with $LiAlH_4$ (0.98 mL of a 1 M solution in Et_2O, 0.98 mmol) overnight then 1.96 mL more $LiAlH_4$ solution (1 M in Et_2O, 1.96 mmol) were added before further reaction overnight to give alcohol intermediate (0.228 g, white foam). Using the procedure described for the synthesis of compound **280**, with the exceptions that 20 mL 80% AcOH were used and the reaction was run at ambient temperature for 3 days, the alcohol intermediate (0.42 mmol) was converted to ketone intermediate as the acetic acid salt (0.229 g, yellow glass). Using the procedure described for the synthesis of compound **281**, with the exception that 0.2 mL DMF were added, the ketone intermediate (0.42 mmol) was converted to the crude alkene. Using the procedure described for the synthesis of compound **282**, the crude alkene was converted to the acetic acid salt. Precipitation from Et_2O afforded compound **298** (0.088 g, 40% from compound **95**) as an orange solid. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 388.05; $C_{24}H_{38}NO_3$.

<u>Synthesis of compound **299**</u>

Using the procedure described for the synthesis of compound **278**, with the exceptions that 0.20 g of 4 Å molecular sieves and 7 mL DCE were used, the

mixture was stirred for 1 hour before $NaB(OAc)_3H$ was added, reaction time was 3 days and the residue was purified by chromatography on silica gel (EtOAc; EtOAc/MeOH/Et_3N, 9:1:0.3), compound **95** (0.25 g, 0.49 mmol) was reacted with ethanolamine (0.15 mL, 2.5 mmol) to give amine intermediate (0.274 g, quantitative, yellow foam). Using the procedure described for the synthesis of compound **279**, the amine intermediate (0.49 mmol) was reacted with $LiAlH_4$ (0.98 mL of a 1 M solution in Et_2O, 0.98 mmol) overnight then 0.98 mL more $LiAlH_4$ solution (1 M in Et_2O, 0.98 mmol) were added before further reaction overnight to give alcohol intermediate (0.224 g, colourless glass). Using the procedure described for the synthesis of compound **280**, with the exceptions that 20 mL 80% AcOH were used and the reaction was run at ambient temperature for 3 days, the alcohol intermediate (0.44 mmol) was converted to ketone intermediate as the acetic acid salt (0.216 g, colourless glass). Using the procedure described for the synthesis of compound **281**, with the exception that 0.5 mL DMF were added, the ketone intermediate (0.44 mmol) was converted to the crude alkene. Using the procedure described for the synthesis of compound **282**, with the exception that the residue was not purified by chromatography, the crude alkene was converted to the acetic acid salt. Concentration from CH_2Cl_2 afforded compound **299** (0.041 g, 20% from compound **95**) as a yellow solid. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 352.06; $C_{21}H_{38}NO_3$.

<u>Synthesis of compound **300**</u>

Using the procedure described for the synthesis of compound **278**, with the exceptions that 0.10 g of 4 Å molecular sieves were used, reaction time was 2.5 days and the residue was purified by chromatography on silica gel (hexanes/EtOAc, 8:2), compound **95** (0.10 g, 0.20 mmol) was reacted with *m*-toluidine (0.10 mL, 0.93 mmol) to give amine intermediate (0.091 g, 77%, yellowish gum). Using the procedure described for the synthesis of compound **279**, with the exceptions that 8 mL THF were used, $LiAlH_4$ solution was added at 0°C and the mixture was stirred at 0°C for 20 minutes before stirring at ambient temperature, and reaction time was 3.5 hours, the amine intermediate (0.15 mmol) was reacted with $LiAlH_4$ (0.45 mL of a 1 M solution in

THF, 0.45 mmol) to give crude alcohol intermediate. Using the procedure described for the synthesis of compound **280**, with the exceptions that 4 mL 80% AcOH were used and reaction time was 5 hours, the crude alcohol intermediate (0.15 mmol) was converted to crude ketone intermediate. Using the procedure described for the synthesis of compound **281**, with the exceptions that 7 mL THF and 0.5 mL DMF were used and after quenching the mixture was diluted with EtOAc (20 mL) and MeOH (5 mL) then filtered through celite, the ketone intermediate (0.15 mmol) was converted to alkene (0.021 g, pale gum). Using the procedure described for the synthesis of compound **282**, with the exception that the residue was not purified by chromatography, the alkene was converted to the acetic acid salt. Precipitation from ACN/MeOH afforded compound **300** (0.020 g, 21% from compound **95**) as a yellow foam.

Synthesis of compound **301**

Using the procedure described for the synthesis of compound **278**, with the exceptions that 0.10 g of 4 Å molecular sieves were used, reaction time was 2.5 days and the residue was purified by chromatography on silica gel (EtOAc/MeOH, 9:1), compound **95** (0.10 g, 0.20 mmol) was reacted with pyrrolidine (0.10 mL, 1.2 mmol) to give amine intermediate (0.090 g, 82%, clear gum). Using the procedure described for the synthesis of compound **279**, with the exceptions that 8 mL THF were used, $LiAlH_4$ solution was added at 0°C and the mixture was stirred at 0°C for 20 minutes before stirring at ambient temperature, and reaction time was 3.5 hours, the amine intermediate (0.16 mmol) was reacted with $LiAlH_4$ (0.45 mL of a 1 M solution in THF, 0.45 mmol) to give crude alcohol intermediate. Using the procedure described for the synthesis of compound **280**, with the exceptions that 4 mL 80% AcOH were used and reaction time was 5 hours, the crude alcohol intermediate (0.16 mmol) was converted to crude ketone intermediate. Using the procedure described for the synthesis of compound **281**, with the exceptions that 7 mL THF and 0.5 mL DMF were used and after quenching the mixture was diluted with EtOAc (20 mL) and MeOH (5 mL), then filtered through celite, the ketone intermediate (0.16 mmol) was converted to alkene (0.029 g, gum). Using the procedure described for the synthesis of compound **282**, with

the exception that the residue was not purified by chromatography, the alkene was converted to the acetic acid salt. Precipitation from ACN/MeOH afforded compound **301** (0.038 g, 42% from INT1703) as an off-white foam. LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 362.18; $C_{23}H_{40}NO_2$.

Synthesis of compound **302**

Using the procedures described for the synthesis of compound **282**, with the exception of substitution by *N,N*-dimethylethylenediamine, compound **302** (0.067 g) was prepared as a orange solid in 39% yield starting from compound **205**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 393.03; $C_{24}H_{45}N_2O_2$.

Synthesis of compound **303**

Using the procedures described for the synthesis of compound **282**, with the exception of substitution by 3,4-(methylenedioxy)aniline, compound **303** (0.055 g) was prepared as a orange solid in 33% yield starting from compound **205**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 441.95; $C_{27}H_{40}NO_4$.

Synthesis of compound **304**

Using the procedures described for the synthesis of compound **282**, with the exception of substitution by cyclohexylamine, compound **304** (0.022 g) was prepared as a light yellow solid in 12% yield starting from compound **205**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 404.05; $C_{26}H_{46}NO_2$.

Synthesis of compound **305**

Using the procedures described for the synthesis of compound **282**, with the exception of substitution by 3-trifluoromethylaniline, compound **305** (0.096 g) was prepared as a white solid in 54% yield starting from compound **205**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 465.45; $C_{27}H_{38}F_3NO_2$.

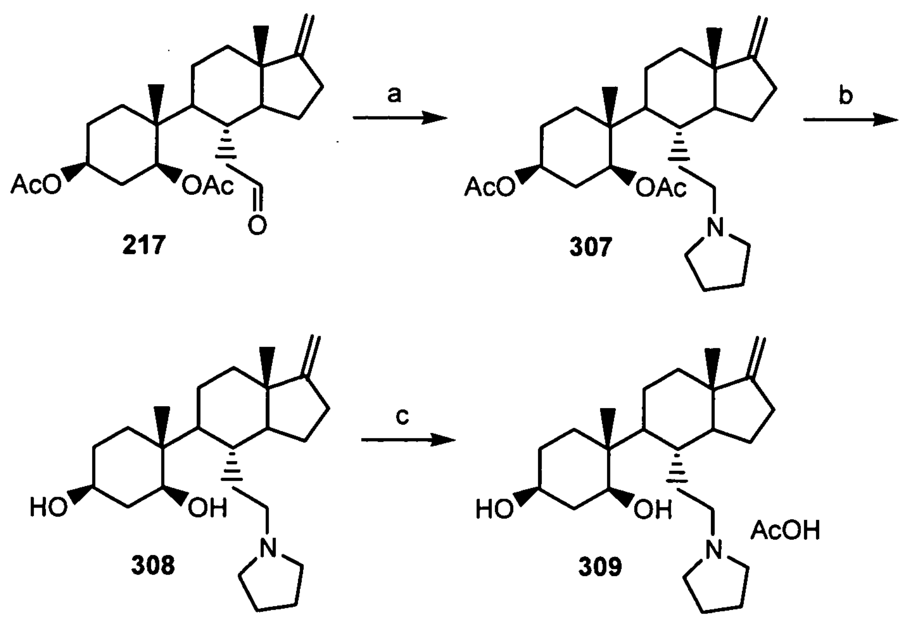
Synthesis of compound **306**

Using the procedures described for the synthesis of compound **282**, with the exception of substitution by isobutylamine, compound **306** (0.035 g) was prepared as a white solid in 21% yield starting from compound **205**: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 378.08; $C_{24}H_{44}NO_2$.

EXAMPLE 36

Compounds **308-310**, representative compounds of the invention, may be prepared according to the following Reaction Scheme 36. Any number of compounds related to compounds **308-310** could be produced using similar methodology. Starting compound **217** may be prepared according to the procedure described above in Example 24.

REACTION SCHEME 36



a) pyrrolidine, NaB(OAc)$_3$H, 4 Å MS, DCE; b) LiAlH$_4$, THF; c) 80% AcOH, MeOH.

In general, reductive amination of compound **217** gives compound **307**. A reducing agent, such as lithium aluminum hydride, is used to reduce the ester-protected

hydroxyls to give compound **305**. Treatment with 80% acetic acid form the ammonium acetate salt of compound **309**.

Synthesis of compound **307**

A mixture of compound **217** (0.20 g, 0.49 mmol), pyrrolidine (0.18 mL, 2.2 mmol) and 4 Å molecular sieves (0.20 g) in DCE (5 mL) was stirred at ambient temperature for 30 minutes. $NaB(OAc)_3H$ (0.297 g, 1.33 mmol) was added, rinsing with DCE (2 mL), and the mixture was stirred at ambient temperature overnight. The reaction mixture was diluted with MeOH (3 mL) and filtered through a celite bed, rinsing with EtOAc (25 mL). The filtrate was washed with saturated $NaHCO_3$ solution (10 mL), then brine (2 x 5 mL), dried over anhydrous $MgSO_4$ and concentrated to give compound **307** (0.235 g, quantitative) as a colourless glass that was used in the next reaction without further purification.

Synthesis of compound **308**

To a solution of compound **307** (0.49 mmol) in THF (10 mL) was added $LiAlH_4$ (0.88 mL of a 1 M solution in THF, 0.88 mmol). The mixture was stirred at ambient temperature overnight, then quenched with $Na_2SO_4 \cdot 10H_2O$ and stirred for 1 hour. The mixture was filtered, rinsing with EtOAc, and concentrated to dryness. The residue was purified by chromatography on silica gel (EtOAc/MeOH, 9:1; EtOAc/MeOH/Et_3N, 9:0.75:0.25) to give compound **308** as a white solid that was used for the next reaction.

Synthesis of compound **309**

A mixture of compound **308**, 80% AcOH (1 mL) and MeOH (5 mL) was concentrated by rotary evaporation. Concentration from CH_2Cl_2 afforded compound **309** (0.168 g, 79% from INT5) as a white foam: LC/MS (direct infusion, electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 375.95; $C_{24}H_{42}NO_2$.

Synthesis of compound **310**

Using the procedures described for the synthesis of compound **309**, with the exception of substitution by *m*-toluidine, compound **310** (0.20 g) was prepared as a yellow foam in 69% yield starting from compound **217**. LC/MS (direct infusion,

electrospray +ve, 10 mM NH_4OAc in 3:7 water and MeCN) 412.01; $C_{27}H_{42}NO_2$.

The following compounds of the invention were prepared according to the foregoing Examples:

Compound **25**; 5-(1β-methyl-4β-hydroxy-2β-(2-hydroxyethyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **29**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **38**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(2-hydroxyethyl)-7aβ-methyl-1-methyleneoctahydroindene;

Compound **45**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **51**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **59**; 5-(1β-methyl-4β-amino-2β-hydroxymethylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **67**; 5-(1β-methyl-4β-hydroxy-2β-(2-aminoethyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **68**; 5-(1β-methyl-4β-hydroxy-2β-(2-aminoethyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-ethylideneoctahydroindene, ammonium acetate salt;

Compound **77**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-aminomethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **78**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **79**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-aminomethyl-1,1-dimethyl-2,3,4,5,6,7-hexahydro-*1H*-indene, ammonium chloride salt;

Compound **80**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium chloride salt;

Compound **81**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-aminomethyl-7aβ-methyl-1-ethylideneoctahydroindene, ammonium chloride salt;

Compound **88**; 5-(1β-methyl-4β-hydroxy-2β-aminomethylcyclohexyl)-4α-

hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **89**; 5-(1β-methyl-4β-hydroxy-2β-aminomethylcyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **100**; 5-(1β-methyl-4β-hydroxy-2β-aminomethylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **101**; 5-(1β-methyl-4β-hydroxy-2β-aminomethylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **107**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(2-aminoethyl)-7aβ-methyl-1-methyleneoctahydroindene;

Compound **108**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(2-aminoethyl)-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **119**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-aminomethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **120**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **132**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-aminomethyl-7aβ-methyl-1-difluoromethyleneoctahydroindene;

Compound **133**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-aminomethyl-7aβ-methyl-1-difluoromethyleneoctahydroindene, ammonium chloride salt;

Compound **143**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-aminomethyl-7aβ-methyl-1-dichloromethyleneoctahydroindene, ammonium chloride salt;

Compound **157**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-aminomethyl-7aβ-methyl-1β-(propen-2-yl)octahydroindene;

Compound **158**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-aminomethyl-7aβ-methyl-1β-(propen-2-yl)octahydroindene, ammonium acetate salt;

Compound **163**; 5-(1β-methyl-4β-hydroxy-2β-(2-hydroxyethyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-3a,4,5,6,7,7a-hexahydro-*3H*-indene;

Compound **178**; 5-(1β-methyl-4α,5α-dihydroxy-2β-

hydroxymethylcyclohexyl)-4α-aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **182**; 5-(1β-methyl-4β-hydroxy-2β-(3-dimethylaminoprop-1-enyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **183**; 5-(1β-methyl-4β-hydroxy-2β-(3-dimethylaminoprop-1-enyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **184**; 5-(1β-methyl-4β-hydroxy-2β-(2-(4-chlorophenyl)ethyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **185**; 5-(1β-methyl-4β-hydroxy-2β-(2-pyridin-3-ylethyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **189**; 5-(1β-methyl-4β-hydroxy-2β-ethylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **192**; 5-(1β-methyl-4β-hydroxy-2β-(2-(4-ethoxyphenyl)eth-1-en-1-yl)cyclohexyl)-4α-acetoxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **195**; 5-(1β-methyl-4β-hydroxy-2β-(2-(pyridin-2-yl)eth-1-en-1-yl)cyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **196**; 5-(1β-methyl-4β-hydroxy-2β-(2-(pyridin-3-yl)eth-1-en-1-yl)cyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **197**; 5-(1β-methyl-4β-hydroxy-2β-(hept-1-en-1-yl)cyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **198**; 5-(1β-methyl-4β-hydroxy-2β-(4-benzyloxybut-1-en-1-yl)cyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **199**; 5-(1β-methyl-4β-hydroxy-2β-(3-dimethylaminoprop-1-en-1-yl)cyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **200**; 5-(1β-methyl-4β-hydroxy-2β-(2-(4-chloropheny)ethenyl)cyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-

methyleneoctahydroindene;

Compound **201**; 5-(1β-methyl-4β-hydroxy-2β-(4-hydroxybut-1-en-1-yl)cyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **203**; 5-(1β-methyl-4β-hydroxy-2β-(3-hydroxyprop-1-en-1-yl)cyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **210**; 5-(1β-methyl-4β-hydroxy-2β-(3-(4-chlorophenyl)prop-2*Z*-en-1-yl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **211**; 5-(1β-methyl-4β-hydroxy-2β-(3-(4-chlorophenyl)prop-2*E*-en-1-yl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **212**; 5-(1β-methyl-4β-hydroxy-2β-(4-dimethylaminolbut-1-en-1-yl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **219**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(4-dimethylaminobut-2*Z*-en-1-yl)-7aβ-methyl-1-methyleneoctahydroindene;

Compound **220**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(4-dimethylaminobut-2*Z*-en-1-yl)-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **221**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(3-pyridin-3-ylprop-2*Z*-en-1-yl)-7aβ-methyl-1-methyleneoctahydroindene;

Compound **222**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(3-pyridin-3-ylprop-2*E*-en-1-yl)-7aβ-methyl-1-methyleneoctahydroindene;

Compound **225**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(methylsulfonyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **227**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(acetyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **229**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(ethyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **231**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(benzyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **232**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-

4α-(benzyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **233**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(cyclopropylmethyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **235**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(dimethyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **236**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(dimethyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **240**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(methyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **241**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(methyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **242**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(guanidino)methyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium chloride salt;

Compound **243**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(2-methylpropyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **244**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(2-methylpropyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **245**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(1-methylpiperidin-4-yl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium diacetate salt;

Compound **246**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(3-nitrobenzyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **247**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-

4α-(piperonyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **248**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(pyrrol-2-ylmethyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **249**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(furfuryl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **250**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(pyridin-3-ylmethyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **252**; 5-(1β-methyl-4β-hydroxy-2β-(pyrrolidin-1-yl)methylcyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **253**; 5-(1β-methyl-4β-hydroxy-2β-(pyrrolidin-1-yl)methylcyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **254**; 5-(1β-methyl-4β-hydroxy-2β-(2-hydroxyethyl)aminomethylcyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **255**; 5-(1β-methyl-4β-hydroxy-2β-(2-dimethylaminoethyl)aminomethylcyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **256**; 5-(1β-methyl-4β-hydroxy-2β-(cyclohexyl)aminomethylcyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **257**; 5-(1β-methyl-4β-hydroxy-2β-(pyridin-3-ylmethyl)aminomethylcyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **258**; 5-(1β-methyl-4β-hydroxy-2β-(furfuryl)aminomethylcyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-

methyleneoctahydroindene, ammonium acetate salt;

Compound **259**; 5-(1β-methyl-4β-hydroxy-2β-(3-fluorophenyl)aminomethylcyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **260**; 5-(1β-methyl-4β-hydroxy-2β-(pyridin-3-yl)aminomethylcyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **261**; 5-(1β-methyl-4β-hydroxy-2β-(3-methylphenyl)aminomethylcyclohexyl)-4α-hydroxymethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **270**; 5-(1β-methyl-4β-hydroxy-2β-hydroxymethylcyclohexyl)-4α-(imidazol-1-yl)methyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **276**; 5-(1β-methyl-4β-hydroxy-2β-(cyclopentyl)aminomethylcyclohexyl)-4α-aminomethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **277**; 5-(1β-methyl-4β-hydroxy-2β-(cyclopentyl)aminomethylcyclohexyl)-4α-aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium diacetate salt;

Compound **282**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(2-methylpropyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **283**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(pyridin-3-ylmethyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **284**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(2-hydroxyethyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **285**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(furfuryl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **286**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(2-dimethylaminoethyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium

acetate salt;

Compound **287**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(2-cyclohex-1-en-1-ylethyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **288**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(2-morpholin-4-ylethyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **289**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(3-methylphenyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **290**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(benzyl)aminomethyl-7aβ-methyl-1-methyleneoctahydroindene;

Compound **291**; 5-(1β-methyl-4β-hydroxy-2β-(3-fluorobenzyl)aminomethylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **292**; 5-(1β-methyl-4β-hydroxy-2β-(morpholin-4-yl)methylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **293**; 5-(1β-methyl-4β-hydroxy-2β-(1,3-benzodioxol-5-yl)aminomethylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **294**; 5-(1β-methyl-4β-hydroxy-2β-(2-methylpropyl)aminomethylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **295**; 5-(1β-methyl-4β-hydroxy-2β-(cyclohexyl)aminomethylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **296**; 5-(1β-methyl-4β-hydroxy-2β-(*N*-phenyl-*N*-methylamino)methylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **297**; 5-(1β-methyl-4β-hydroxy-2β-(pyridin-3-ylmethyl)aminomethylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **298**; 5-(1β-methyl-4β-hydroxy-2β-(furfuryl)aminomethylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **299**; 5-(1β-methyl-4β-hydroxy-2β-(2-hydroxyethyl)aminomethylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **300**; 5-(1β-methyl-4β-hydroxy-2β-(3-methylphenyl)aminomethylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **301**; 5-(1β-methyl-4β-hydroxy-2β-(pyrrolidin-1-yl)methylcyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **302**; 5-(1β-methyl-4β-hydroxy-2β-(2-(2-dimethylaminoethyl)aminoethyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **303**; 5-(1β-methyl-4β-hydroxy-2β-(2-(1,3-benzodioxol-5-yl)aminoethyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **304**; 5-(1β-methyl-4β-hydroxy-2β-(2-(cyclohexyl)aminoethyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **305**; 5-(1β-methyl-4β-hydroxy-2β-(2-(3-trifluoromethylphenyl)aminoethyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene;

Compound **306**; 5-(1β-methyl-4β-hydroxy-2β-(2-(2-methylpropyl)aminoethyl)cyclohexyl)-4α-hydroxy-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **308**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(2-pyrrolidin-1-ylethyl)-7aβ-methyl-1-methyleneoctahydroindene;

Compound **309**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(2-pyrrolidin-1-ylethyl)-7aβ-methyl-1-methyleneoctahydroindene, ammonium acetate salt;

Compound **310**; 5-(1β-methyl-2β,4β-dihydroxycyclohexyl)-4α-(2-(3-methylphenyl)aminoethyl)-7aβ-methyl-1-methyleneoctahydroindene.

All compounds of the invention as prepared above which exist in free base or acid form may be converted to their pharmaceutically acceptable salts by treatment with the appropriate inorganic or organic base or acid. Salts of the compounds prepared above may be converted to their free base or acid form by standard techniques.

UTILITY EXAMPLES

EXAMPLE A

EFFECT OF COMPOUNDS ON EAR EDEMA IN A TH1 MOUSE MODEL OF CHEMICAL HAPTEN DELAYED TYPE HYPERSENSITIVITY

Delayed type hypersensitivity models are T cell dependent responses. The type of chemical hapten used can bias the T cell response towards a predominantly TH1 or TH2 polarization. Oxazolone and di-nitro-chloro-benzene (DNCB) induce a TH1 dominant immune response.

Mice are sensitized on day 0 by epicutaneous application of 100 μL 3% oxazolone solution in 95% ethanol on the shaved abdomen. This procedure is repeated on day 1. Six days after sensitization (*i.e.*, on day 5), mice are challenged by topically painting 25 μL 0.8% oxazolone dissolved in 95% ethanol on both sides of the right ears and 25 μL of 95% ethanol on the left ears. On day 6 (24 hours after challenge), mice are sacrificed, both ears are removed and a standard disc of tissue is harvested immediately from each ear using a cork borer. Care is taken to sample the tissues from the same ear area. The weight of the ear disc tissues is immediately measured. Test compounds are administered orally at a dose of 5 mg/kg once daily for 7 days (from day 0 to day 6) with the last dose 2 hours prior to sacrifice.

Alternatively, mice are sensitized on day 0 by epicutaneous application of

50 µL 1% di-nitrochlorobenzene (DNCB) solution in 4: ratio of acetone:olive oil on the shaved abdomen. This procedure is repeated on day 5. Starting eleven days after the initial sensitization, mice are challenged 3 times (on days 10, 11, and 12) by topically painting 25 µL 0.5% DNCB dissolved in a 4:1 ratio of acetone:olive oil on both sides of the right ears and 25 µL of vehicle on the left ears. Twenty-four hours after challenge, mice are sacrificed as described above. Test compounds are administered orally at a dose of 10 mg/kg once daily for 5 days (from day 8 to day 12) with the last dose 2 hours prior to challenge.

Ear edema is expressed as increase in ear weight, and calculated by subtracting the left ear weight (challenged with vehicle) from that of right ear (challenged with chemical hapten). The percentage inhibition of the ear edema by drugs is calculated using following equation: 100-((drug edema/mean control edema)*100).

Compounds of the invention may be tested in this assay to show their ability to inhibit oxazolone and DNCB induced dermal inflammation.

EXAMPLE B

EFFECT OF COMPOUNDS ON EAR EDEMA IN A TH2 MOUSE MODEL OF DELAYED TYPE HYPERSENSITIVITY TO FLUORESCEIN ISOTHIOCYANATE

Mice are sensitized on day 0 by epicutaneous application of 50 µL 0.5% fluorescein isothiocyanate (FITC) solution in 1:1 acetone and dibutyl phthalate on the shaved abdomen. This procedure is repeated on day 7. Fourteen days after sensitization (*i.e.*, on day 13), mice are challenged by topically painting 25 µL 0.5% FITC dissolved in 1:1 acetone and dibutyl phthalate on both sides of the right ears and 25 µL 1:1 acetone and dibutyl phthalate solution on the left ears. On day 14 (24 hours after challenge), mice are sacrificed, both ears are removed and a standard disc of tissue is harvested immediately from each ear using a cork borer. Care is taken to sample the tissues from the same ear area. The weight of the ear disc tissues is immediately measured. Test compounds (5-10 mg/kg) or vehicle is administered orally

once daily for 3 days (from day 11 to day 13) 2 hours prior to challenge.

Ear edema is expressed as increase in ear weight, and calculated by subtracting the left ear weight (challenged with vehicle) from that of right ear (challenged with FITC). The percentage inhibition of the ear edema by drugs is calculated using the following equation: 100-((drug edema/mean control edema)*100).

Compounds of the invention, when tested in this assay, were shown to inhibit FITC induced dermal inflammation at doses of less than 20 mg/kg.

EXAMPLE C

EFFECT OF COMPOUNDS ON LPS-INDUCED PERITONITIS IN MOUSE

Mice are administered drug (5 mg/kg) or vehicle orally q.d. for four days with the last dose 2 hours prior to challenge. On day 4, mice are challenged with either saline or lipopolysaccharide (LPS) dissolved in saline (4 mg/kg) via intra-peritoneal injection. At 24h or 48h post challenge, animals are anesthetized, and euthanized by trans-thoracic cardiac exsanguination. The peritoneal cavity is lavaged with ice-cold EDTA containing phosphate buffered saline (PBS). The peritoneal lavage fluid is centrifuged and the supernatant removed. The pellet is resuspended in PBS at 4°C. Cytospins are prepared and stained for manual differentiation and enumeration of cell types. In addition, the resuspended lavage fluid is analyzed for absolute cell numbers and cell differentials by the CellDyn 3700SC hematology analyzer (Abbott Laboratories Inc.).

Compounds of the invention, when tested in this assay, were shown to inhibit LPS induced peritoneal inflammation at doses of less than 20 mg/kg.

EXAMPLE D

EFFECT OF COMPOUNDS ON CARTILAGE DEGRADATION IN MICE

This model is used to investigate the effect of novel compounds on cartilage degradation induced by the natural inflammatory response created by

implantation of a foreign body. Activity in this model may be indicative of activity in arthritis.

Zyphoid sternum cartilage is excised from CO_2 terminated rats, washed in Hibitane, and rinsed in sterile, phosphate buffered saline. A 4 cm diameter disc is removed from the sternum with a # 4 stainless steel leather hole punch, and cut in half. Each half is weighed and wrapped in pre-weighed, moist, sterile cotton before implantation. A piece of cotton wrapped cartilage is implanted subcutaneously into each dorsolateral surface of anaesthetized female CD/1 mice (aged 6 – 8 weeks) via a 1 cm incision along the dorsal midline (Day 0). Mice are administered test articles by oral administration on days 3 to 17. On day 18, mice are sacrificed, the cotton and cartilage removed, and the cartilage separated from the cotton. Both the cartilage and the cotton are weighed, and differences between pre and post implant weights are calculated. The cotton is rinsed in 1mL of buffer, and cytospins are prepared and stained for differentiation and enumeration of cell types. In addition, the resuspended lavage fluid is analyzed for absolute cell numbers and cell differentials by the CellDyn 3700SC hematology analyzer (Abbott Laboratories Inc.).

The cartilage is digested overnight in a papain and cysteine hydrochloric acid solution at 65°C and glucosaminoglycan content remaining in the cartilage is assayed by spectrophotometrically and calculated as %GAG/mg of cartilage degraded (normalized to pre implant cartilage weight).

Compounds of the invention may be tested in this assay to show their ability to inhibit cartilage degradation.

EXAMPLE E

EFFECT OF COMPOUNDS ON IRRITANT-INDUCED MOUSE EAR EDEMA

A number of mice are uniquely identified by placing a mark with an indelible marker on their tail. Mice are dosed orally with 15 mg/kg test compound in 100 μL of 45% β-cyclodextrin in saline. Mice are briefly anaesthesized with 2% halothane, and 2 μg of phorbol 12-myristate 13-acetate (PMA) in 25 μl of acetone is applied to the

inner and outer sides of the left ear of the mouse. Acetone is applied to the right ear of the mouse in the same manner to serve as a vehicle control. Control animals receive the same treatment but without any test compound. After 3 hours, mice are sacrificed by cervical dislocation, and a standard sized biopsy is excised from the ears and weighed to the nearest 1/10th of a mg. Data are analyzed by taking the difference of each left ear from the right ear, and then calculating the % inhibition of edema by (((mean Rx/mean irritant))x100)-100.

Compounds of the invention may be tested in this assay to show their ability to inhibit PMA induced dermal edema.

EXAMPLE F

EFFECT OF COMPOUNDS ON CYTOKINE-INDUCED TRANSENDOTHELIAL MIGRATION OF LEUKOCYTES

The Flow Chamber assay allows for an *in vitro* analysis of the effects of test compounds on leukocyte adhesion to human endothelium. Using a parallel plate flow chamber, human blood is perfused at physiological rates across an inflamed HUVEC monolayer.

HUVEC monolayers are prepared at passage 3 in 35mm tissue culture dishes coated with 2% gelatin and 5μg/mL fibronectin. Following 3 days, confluent monolayers are treated with 25μg/mL of TNF-α for 4 hours. Test compound is added as required for appropriate incubation times (10 min or 4hr). Blood is collected from healthy human adults, drawn into Vacutainers with sodium heparin, and maintained at 37°C. Blood is treated with various concentrations of test compound for 10 min at 37°C. The whole blood is then perfused through the flow chamber for 2 min at a shear force of 10 dynes/cm^2. Monolayers are then washed with HBSS at 37°C for approximately 6 min at 10 dynes/cm^2. Monolayers are video taped at the start of the wash period. During the last 5 min of the wash period, rolling, adherent, and transmigrated leukocytes are manually counted at 20X objective within two fields of view every minute. Adherent leukocytes are defined as being stationary for a minimum of 10 seconds. Data from

each minute is averaged and defined as a percent inhibition against the vehicle treated, TNF-α stimulated, sample. Efficacy of drug articles is compared to a gold standard control sample prepared by treating a HUVEC monolayer with an anti-human E-selectin antibody (10μg/mL) and the blood with a rat anti-human CD18 antibody (20μg/mL), both for 10 min at 37°C.

Compounds of the invention, when tested in this assay, were shown to inhibit TNF-α induced transendothelial migration at concentrations of less than 20 μM.

EXAMPLE G

EFFECT OF COMPOUNDS ON ALLERGEN-INDUCED LUNG INFLAMMATION IN THE RAT

The ability of a compound to inhibit the allergen-induced accumulation of inflammatory cells such as eosinophils and neutrophils in the lavage fluid obtained from sensitized animals is indicative of that compound's anti-asthma activity. In particular, this model system is useful in the evaluation of the effects of a test compound in the treatment of the late phase response of asthma, when lung inflammation and the second phase of bronchoconstriction is apparent, and in allergy, especially where it affects the respiratory system. The test is conducted as follows.

Male Brown Norway rats are sensitized to ovalbumin by single intraperitoneal injection of 1 mg ovalbumin adsorbed to 100 mg $Al(OH)_3$ (alum) in 1 mL sterile saline (saline control rats receive only sterile saline) on day 1, and allowed to sensitize until day 21. Test compounds are given orally q.d. for three days prior to challenge (days 19, 20, 21), and one day post challenge (day 22), with the third dose given 2 hours before challenge, and the fourth day dose given 24 hours after challenge (volume = 300 μl/dose). Rats are challenged with 5% ovalbumin in saline generated using a Devillbis nebulizer for 5 min on day 21.

Forty-eight hours after challenge, animals are sacrificed with an overdose of intraperitoneally-delivered sodium pentobarbitol and the lungs are lavaged with cold 2x7 mL phosphate buffered saline. The recovered lavage fluid is placed on ice. The bronchoalveolar lavage fluid is centrifuged and the supernatant removed. The pellet is

resuspended in phosphate buffered saline at 4°C. Cytospins are prepared and stained for differentiation and enumeration of cell types. Compounds of the invention were shown to inhibit allergen induced lung inflammation at doses of less than 20 mg/kg.

Compounds of the invention, when tested in this assay, were shown to inhibit allergen induced lung inflammation at doses of less than 20 mg/kg.

EXAMPLE H

EFFECT OF COMPOUNDS ON ALLERGEN-INDUCED BRONCHOCONSTRICTION IN THE MOUSE

The Buxco murine airway hyper-responsiveness (AHR) model has been well characterized by numerous investigators, and mimics the severe airway constriction in response to aerosol challenges that sensitized animals exhibit compared to unsensitized animals. The Buxco system uses a technique called whole body plethysmography, in which breathing-induced changes in chamber pressure are quantified using the correlation between increased airway resistance and increased expiratory time/breathing pause to calculate the degree of airway constriction (Penh). Following allergen sensitization and inhalation challenge of the airway, the Penh will increase compared to sham sensitized, sham challenged animals. Thus the effectiveness of a potential anti-inflammatory agent can be determined by examining its impact on ovalbumin induced AHR.

Female Balb/c mice are sensitized on day 1 and 14 by i.p. injection of 100 µL sterile saline containing 20 µg ovalbumin and 2.25 mg $Al(OH)_3$. Sham sensitized mice receive 100 µL sterile saline alone. Test compounds (5 mg/kg) are administered by oral gavage on five consecutive days, two days before challenge (days 26 and 27) and on the three days of ovalbumin challenge (days 28, 29 and 30, 2 hours before challenge). Mice are challenged with aerosolized ovalbumin (5 % in saline) for 20 min on days 28, 29 and 30. On day 31, mice are placed in the whole body plethysmography chambers of the Buxco system and airway reactivity to aerosolized PBS and methacholine (MCh; 0.78, 1.56, 3.125, 6.25, 12.5, 25, 50 mg/mL) challenge is measured as Penh.

Compounds of the invention, when tested in this assay, were shown to inhibit allergen induced airway hyper-reactivity at doses of less than 20 mg/kg.

EXAMPLE I

EFFECT OF COMPOUNDS ON LPS -INDUCED ACUTE LUNG INFLAMMATION IN RAT

Rats are administered drug (1–20 mg/kg) or vehicle orally q.d. for four days prior to challenge. On day 4, rats are challenged with either saline or LPS dissolved in saline (2 mg/kg) via intra-tracheal installation. Animals are sacrificed via intra-peritoneal sodium pentobarbitol overdose 3 hours post challenge, and the lungs lavaged with 14 mL of phosphate buffered saline (PBS). The lung lavage fluid is centrifuged at 300*g* for 3 min, and the supernatant removed. The pellet is resuspended in 1-3 mL of PBS at 4°C depending on pellet size and numbers of total leukocytes. A volume of the final cell suspension, containing approximately 240,000 cells, is added to an appropriate volume of PBS at 4°C to give a final volume of 220 µL and a final concentration of 1 x 10^6 cells/mL (final Cytospin suspension). A 100 µL sample (100,000 cells) is loaded onto a cytospin centrifuge and spun for 4 min at 55*g*. Two slides are prepared per lavage sample, and are fixed and stained in DifQuik. In addition, the resuspended lavage fluid is analyzed for absolute cell numbers and cell differentials by the CellDyn 3700SC hematology analyzer (Abbott Laboratories Inc.).

Compounds of the invention, when tested in this assay, were shown to inhibit LPS induced lung inflammation at doses of less than 20 mg/kg.

EXAMPLE J

EFFECT OF COMPOUNDS ON LPS -INDUCED ACUTE LUNG INFLAMMATION IN MOUSE

Mice are administered drug (1–20 mg/kg) or vehicle orally q.d. for four days prior to challenge. On day 4, mice are challenged with either saline or LPS dissolved in saline (0.15 mg/kg) via intra-tracheal installation. Animals are sacrificed using an intra-peritoneal sodium pentobarbitol overdose 6 hours post challenge. After

thoracotomy, lungs are lavaged with 3 x 0.75 mL of PBS. The bronchoalveolar lavage fluid is centrifuged and the supernatant removed. The pellet is resuspended in PBS at 4°C. Cytospins are prepared and stained for differentiation and enumeration of cell types. In addition, the resuspended lavage fluid is analyzed for absolute cell numbers and cell differentials by the CellDyn 3700SC hematology analyzer (Abbott Laboratories Inc.).

Compounds of the invention may be tested in this assay to show their ability to inhibit LPS induced lung inflammation.

EXAMPLE K

EFFECT OF COMPOUNDS ON PROSTAGLANDIN E2 SYNTHESIS

Prostaglandin E2 (PGE2) is a primary product of arachidonic acid (AA) metabolism. Like most eicosanoids, it does not exist preformed in cellular reservoirs. PGE2 synthesis is catalyzed by cyclooxygenase-2 (COX-2), an inducible enzyme up-regulated by inflammatory stimuli, cytokines and mitogens. COX-2 up-regulation results in increased PGE2 production. Elevated concentrations of PGE2 have been reported in chronic inflammatory conditions such as rheumatoid arthritis and asthma. Inhibition of COX-2 and PGE2 synthesis would be a major target for the future treatment of inflammatory arthropathies.

Human umbilical vein endothelial cells (HUVEC-C) are grown to confluency in gelatin coated plates in the presence of endothelial growth medium (EGM-2). EGM-2 is replaced with RPMI-1640 medium containing 2% fetal bovine serum (FBS) for the assay. HUVEC-Cs are incubated with the tested compounds for 1 hour before stimulation with IL-1β for 24 hours. Exogenous AA is added for 15 minutes and PGE2 concentration in cell culture supernatants is determined by a competitive enzyme immunoassay (EIA).

The compounds are dissolved at a concentration of 20 mM in DMSO, and tested in the assay at 5 and 1μM with final DMSO concentration of 0.05%. Samples are tested in triplicates. Controls included in each experiment are: untreated cells, IL-1β

treated cells, NS-398/IL-1β treated cells and a standard curve of known concentrations of PGE2. NS-398 is a selective inhibitor of COX-2 activity. PGE2 concentration is calculated by log-logit curve fit software and plotted versus PGE2 concentration in a standard curve.

Percent inhibition is calculated as: $\% I = 100 - [PGE2]_C / [PGE2]_{Co} \times 100$, where $[PGE2]_C$ is the concentration of PGE2 in compound/IL-1β treated samples and $[PGE2]_{Co}$ is the concentration of PGE2 in IL-1β treated sample.

Compounds of the invention were shown to inhibit PGE2 synthesis at concentrations of less than 10 μM.

* * * * *

All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.